Thesis Presented for the Degree of

DOCTOR OF PHILOSOPHY

In the Faculty of Humanities

Relationships between Psychosocial Stress, Cortisol, Apolipoprotein ϵ4, Beta-Amyloid, Hippocampal Volume, and Alzheimer's Disease in a Sample of South African Older Adults

Katharine Ann James

JMSKAT002

Department of Psychology

UNIVERSITY OF CAPE TOWN

August 2013

It is not by muscle, speed, or physical dexterity that great things are achieved, but by reflection, force of character, and judgement; in these qualities old age is usually not only not poorer, but is even richer.

~ Marcus Tullius Cicero (106-43 BC)

Declaration

I hereby declare that this dissertation is my own unaided work, both in concept and execution. To the best of my knowledge and belief this dissertation contains no material written by another person, except where due acknowledgement has been made in the text. Neither the substance nor any part of the above thesis has been submitted in the past, or is being, or is to be submitted for a degree at this University or at any other university, except as stated below:

Laurian Grace, a fellow PhD candidate and researcher on this project, has included in her own PhD dissertation some of the apolipoprotein ϵ4 and cognitive scores data that I present in my thesis. However, we included different participants to a certain degree and we investigated these data in terms of different research questions relating to varying factors of interest in our respective theses.

_____ _____

Katharine A. James Date

Acknowledgements

Completion of this PhD dissertation would not have been possible without the support and encouragement of many. To them, I dedicate this:

Associate Professor Kevin Thomas, my supervisor from the Department of Psychology, University of Cape Town, for enrolling me in this project in my Honours year and opening the door for me into an area of psychological science which I have found to be immensely interesting, challenging, and rewarding. I thank him for his encouragement and support of independent research, his assistance and advice throughout, and his impeccable attention to detail.

Associate Professor Marc Combrinck, from the Divisions of Neurology and Geriatric Medicine, Department of Medicine, Groote Schuur Hospital/University of Cape Town. A/Prof Combrinck was the principal investigator on this research study and my co-supervisor. He provided invaluable resources, assistance, and guidance throughout the project. I am indebted to him for his passion regarding neuroscience and geriatric medicine and the countless hours he spent teaching me in these areas. I largely owe my interest in this field to him.

Ms Laurian Grace, fellow researcher and PhD candidate on this study. We walked this road together and I am extremely grateful for the shared journey; including the frustrations, trials and tears, but also the laughter, friendship, support, and personal growth.

Sister Jacqui Raphahlelo, for her help with contacting participants, arranging clinical visits, assisting with the assessment of participants, and processing biological samples.

Drs Marc Combrinck, Helen Cross, Elana van Brakel, and Ilhaam Mohammed for their assistance in performing the medical examinations of the participants.

Dr Chris Warton for training me in the manual tracing of brain structures on MRI scans and for his assistance in tracing and determining hippocampal volumes.

Professor Ernesta Meintjies, Dr Stefan du Plessis, Mrs Nailah Maroof, and the Cape Universities Brain Imaging Centre for their assistance with neuroimaging and post-processing.

Dr Judith Hornby and Ms Lindsay Petersen, from the Centre for Proteomic & Genomic Research, for running the Bioplex assay and allowing me to observe and understand the process.

Ms Felicity Leisegang, the medical scientist at the IMD Laboratory, Chemical Pathology, National Health Laboratory Service, who performed the PCR analyses for determination of the apolipoprotein genotypes of the participants and for allowing me to observe the PCR process.

The members of the ACSENT Laboratory in the Department of Psychology for their guidance and input regarding several stages of my project.

The Division of Neurology at Groote Schuur Hospital for providing the research fellowship to enable me to undertake this study and for the guidance and suggestions provided.

The National Research Foundation and the University Research Committee for funding this study and for providing travel grants; these provided me with the opportunity to disseminate my preliminary findings to local and international audiences, and to network with experts in the fields of neurodegenerative diseases and Alzheimer's disease.

My family, who mean more to me than words could express: my parents, Mike and Debbie, and my brothers, David and Chris, who unfailingly support and believe in me and who inspire me to take on challenging tasks and push my own boundaries. Their encouragement was invaluable.

My friends, old and new, far and near, for supporting me every step of the way.

Last, but certainly not least, the study participants and their families for their role in, and invaluable contribution to, this research.

Abbreviations

ACTH	-	adrenocorticotrophic hormone
Aβ	-	beta-amyloid
AD	-	Alzheimer's disease
ADAS-cog	-	Alzheimer's Disease Assessment Scale-cognitive subscale
APOE	-	Apolipoprotein
APP	-	amyloid precursor protein
BACE1	-	beta-site APP cleaving enzyme 1
BADLS	-	Bristol Activities of Daily Living Scale
BMI	-	Body Mass Index
CAMCOG-R	-	Cambridge Cognitive Examination-Revised
CD-RISC	-	Connor-Davidson Resilience Scale
χ^2	-	Chi-square
CLOX	-	Executive Clock Drawing Task
CRH	-	corticotrophin-releasing hormone
CRF	-	corticotrophin-releasing factor
CSF	-	cerebrospinal fluid
CUBIC	-	Cape Universities Brain Imaging Centre
DECO	-	Deterioration Cognitive Observee
DSM-IV-TR	-	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition-Text Review
GDS	-	Geriatric Depression Scale
GLM-RM	-	general linear model-repeated measures
GP	-	general practitioner
GSH	-	Groote Schuur Hospital
Є	-	epsilon
HIC	-	high income country
HPA	-	hypothalamic pituitary adrenal
HV	-	hippocampal volume
ICC	-	Intraclass Correlation Coefficient
ICV	-	intracranial volume
LAMIC	-	low- and middle-income country
LTE-Q	-	List of Threatening Life Events Questionnaire
MCI	-	mild cognitive impairment
MMSE	-	Mini Mental State Examination
MRC	-	Medical Research Council
MRI	-	Magnetic Resonance Imaging
Nmol/L	-	nanomoles per litre
η_p^2	-	partial eta squared
NINCDS/ADRDA	-	National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association
PET	-	positron emission tomography
Φ	-	Phi
PROSPER	-	Prospective Study of Pravastatin in the Elderly at Risk
PS1	-	Presenilin 1
PS2	-	Presenilin 2

PSS	-	Perceived Stress Scale
p-tau	-	phosphorylated tau
PTSD	-	post-traumatic stress disorder
SEM	-	structural equation model
SES	-	socioeconomic status
Tg	-	transgenic
TMT	-	Trail Making Test
TPT	-	The Placing Test

Table of Contents

List of Figures

List of Tables

ABSTRACT

Background: Many factors contribute to age-related changes in cognitive functioning. There is no single defined profile of factors that is clearly associated with the presence, or rate of progression, of cognitive changes in older adults. Stress, both psychosocial and physiological, may play a role. **Aims:** The general aim of this study was to explore the relationships between cognitive functioning and cognitive decline, on the one hand, and psychosocial and physiological stress, as well as a range of sociodemographic, psychosocial and physiological factors, on the other, in older adults with a range of cognitive function including healthy and impaired. **Methods:** Both cross-sectional (Study 1) and longitudinal (Study 2) designs addressed these aims. Study 1 examined the contribution of stress and sociodemographic, psychosocial, and physiological factors to cognition. Participants were 69 cognitively healthy older adults and 65 possible or probable Alzheimer's disease (AD) patients. They were all over the age of 60 and resided in the greater Cape Town metropolitan region of South Africa. Cognitive functioning was assessed using a battery of neuropsychological tests. Salivary cortisol levels, apolipoprotein E (APOE) genotype, and plasma beta-amyloid levels were determined at baseline. A subset of participants underwent magnetic resonance imaging to determine brain hippocampal volumes. Study 2 investigated whether any of the variables measured at baseline were significant predictors of cognitive change and cognitive decline over a three-year period. **Results:** In the cross-sectional study, a hierarchical regression model showed that older age, fewer years of education, and the presence of the APOE ϵ4 allele were predictors of poorer cognitive function. Although cognitive function was not significantly associated with either psychosocial stress or morning salivary cortisol levels (a physiological marker of stress), AD patients had significantly higher levels of self-perceived psychosocial stress. Secondary statistical analyses also showed a moderately positive association between morning salivary cortisol levels and the ratio of beta-amyloid 1-42/-40 concentrations. Furthermore, AD patients had smaller hippocampal volumes than controls, and AD patients with the ϵ4 allele had smaller hippocampal volumes than patients without. Across the entire sample, hippocampal volumes were associated with cognitive functioning. In the longitudinal study, baseline cognitive measures (as taken in Study 1) were compared with two subsequent annual assessments (Time 1 and Time 2). Across the entire sample, only age and education predicted cognitive change across time, and none of the predictor variables was associated with cognitive decline across the same time period. **Conclusions:** The profile of factors associated with cognitive functioning in this sample of older South African adults was similar to that found in studies from high-income countries. In this study, stress was not related to baseline cognitive function or to subsequent cognitive decline. This study is novel for South Africa and contributes to our knowledge of cognitive ageing and AD in low- and middle-income countries. It highlights the importance of age-associated cognitive disorders for public health on a continent in which they have largely been ignored.

CHAPTER ONE: GENERAL INTRODUCTION

The central theme of this doctoral dissertation is the contribution of stress to cognitive functioning in South African older adults across a spectrum of cognition in healthy older adults and in those with cognitive impairment in Alzheimer's disease (AD). The effects of biological factors on age-related cognitive functioning have been widely studied. However, the role of psychosocial factors such as stress for cognitive functioning is less well known. Stress, and the experience of traumatic life events, have negative consequences for mental health (Williams et al., 2007). More specifically, the experience of stress appears to be associated with mild cognitive impairment (MCI) and with risk for developing Alzheimer's disease (Catania et al., 2009; Peavy et al., 2012; Wilson et al., 2007).

Investigating the contribution of stress to age-related cognitive functioning is especially relevant in the South African context. South Africa has a turbulent socio-political history, high levels of crime and violence, and elevated rates of exposure to traumatic life events and psychosocial stress (Finchilescu & Dawes, 1999; Williams et al., 2007). South African adults are likely to have experienced multiple traumatic events during their life which may have enduring effects on cognition. Thus it is pertinent to examine the effects of such psychosocial stress on cognitive functioning in these older adults.

Although my core focus was on stress, I also aimed to explore the relationships of several factors with cognitive impairment and subsequent cognitive decline in older South African adults. These factors were chosen because they have previously been identified as risk factors for AD. However, the aim of this thesis was not to explore these factors in terms of their risk for cognitive impairment and AD, but rather to examine their associations with cognitive functioning and cognitive change/decline across a spectrum of healthy cognition to impaired cognition such as in AD. To this end, I embarked upon two studies: one cross-sectional (Study 1) and the other longitudinal (Study 2).

The aim of Study 1 was to investigate the relationship between psychosocial stress, cortisol, the apolipoprotein E (APOE) ϵ4 allele, beta-amyloid (Aβ), hippocampal volume, and cognitive functioning in a sample of cognitively healthy older adults and

AD patients. I chose to examine the relationships between factors that previous research has shown to be associated with (a) cognitive impairment in AD and (b) the experience of stress. Such an examination allowed me to perform integrative research to advance understanding of numerous factors that might affect cognitive functioning in older adults. Undertaking this exploration required an interdisciplinary approach, and so my research methods spanned the fields of psychology, physiology, biochemistry, and neuroradiology. By looking at different types of stress (e.g., recent, remote, and total psychosocial stress, and physiological stress as measured by cortisol), and their relationships with one another and with other physiological variables, I hoped to further current knowledge of stress and its impact on cognitive functioning in normal ageing and in AD.

The aim of Study 2 was to identify variables associated with cognitive change and cognitive decline. That is to say, I sought to explore factors measured at baseline and their association with subsequent cognitive change/decline.

An important note here is that a definitive diagnosis of AD can only be made with post-mortem histopathological confirmation of the disease (Chintamaneni & Bhaskar, 2012). Thus, all references in this dissertation to AD and AD patients refer to possible or probable AD, according to the clinical criteria stipulated by the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) (McKhann et al., 1984), and by the fourth edition (text revision) of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) (American Psychiatric Association, 2003).

Ultimately, I aimed to integrate results from the cross-sectional and longitudinal studies to provide a picture of factors that (a) were associated with baseline cognitive functioning in older South African adults, (b) predicted subsequent cognitive change/decline, and (c) were associated with both baseline cognitive functioning and subsequent cognitive change/decline. Thus, I begin with a general introduction (*Chapter One*) in which I discuss the concept of stress and provide an overview of AD. I then move on to discuss the literature, methods, and results for Study 1, followed by a brief summary of those results (*Chapter Two*). I then discuss the literature, methods, and results for Study 2, followed by a brief summary of those results (*Chapter Three*). Finally, I interpret and discuss the findings from both studies in a general discussion (*Chapter Four*).

Such investigation of the combination of these factors provides a novel contribution to the literature. These factors and their relation to cognition have been explored either on their own, or alongside only a few other factors. To my knowledge, no single study has attempted simultaneous investigation of all of these factors and their relationship to cognition in older adults. This contribution to knowledge is especially relevant in low- or middle-income countries (LAMICs), where little data regarding age-related diseases in older adults are available. The 10/66 Dementia Research Group estimates that two-thirds of the world's estimated 24 million people with dementia live in LAMICs, but that less than one-tenth of all population-based research into dementia and AD has been performed in developing countries (Prince, 2000). Although some such data do exist for LAMICs (e.g., in India, China and southeast Asia, Latin America and the Caribbean, and Africa; (Chandra et al., 1998; Hendrie et al., 1995; Mathuranath et al., 2012; Prince, Acosta, Chiu, Scazufca, & Varghese, 2003; Scazufca et al., 2008; Shaji, Bose, & Verghese, 2005), there is a paucity of this kind of research in South Africa. Such research is important in South Africa, because, despite the high prevalence of HIV/AIDS and other infectious diseases (Corbett et al., 2002; Muula, 2008), the South African population is ageing rapidly (Joubert & Bradshaw, 2006) and the country has one of the highest proportions of older persons in Africa (Kinsella & Ferreira, 1997).

What is Stress?

Providing a concise definition of stress is problematic because the current scientific literature contains varying explanations. Broadly speaking, however, stress can be considered as a stimulus, as a reaction to a stimulus, or as the physiological effects of that reaction (Kemeny, 2013).

Within one frequently cited framework, the neurobiological stress response occurs as a result of stressors (i.e., life experiences that threaten a primary goal). By this definition, stressors are categorized as being either physiological (i.e., presenting a threat to one's physical integrity) or psychological (i.e., presenting a threat to one's mental well-being) in nature (Dickerson, Gruenewald, & Kemeny, 2004; Stawski, Sliwinski, & Smyth, 2006).

A key figure in stress research, Hans Selye, a distinguished physician and endocrinologist, coined the word "stress". In his book, 'The Stress of Life" Selye

provides a more functional definition of stress stating that it is "the state manifested by a specific syndrome which consists of all the nonspecifically-induced changes within a biologic system" (Selye, 1976, p. 64). Hence, he suggests that stress has its own constitution, but without one particular cause, that produces visible changes in response to stress. Selye writes about the General Adaptation Syndrome, in which he describes the stereotypical response pattern that occurs in situations of stress. Stated simply, this pattern includes an initial shock phase and an alarm reaction, followed by adaptation to the stressor, followed by an exhaustion phase, where persistent aversive stimulation can overcome an organism's ability to resist the stressor (Selye, 1976).

Stress is linked to disease because it disrupts one's natural balance, homeostasis, which is vital for health and well-being (Perry & Pollard, 1998). An American physiologist, Cannon (1932, pg. 24), described homeostasis as "a condition which may vary, but which is relatively constant". Homeostasis is considered to be incorporated by allostasis in relation to the life cycle of an organism and its individual experiences and responses to the surrounding environment (McEwen & Wingfield, 2010). The concept of allostasis, which means "maintaining stability or homeostasis through change", was introduced by Sterling and Eyer (1988). It essentially relates to adaptive processes that sustain homeostasis through facilitators that include, primarily, adrenalin and cortisol (McEwen, 2005). These chemical messengers, adrenalin and cortisol, encourage adaptation in the response to acute stress; however, they can also result in allostatic load. Allostatic load, an indicator of the cumulative toll taken on the body, refers to wear and tear as a result of repeated exposure to chronic stress (McEwen & Seeman, 1999). A high allostatic load might result from chronic overactivation of the stress system (Juster, McEwen, & Lupien, 2010; McEwen, 1998; McEwen & Stellar, 1993). When an organism is exposed to prolonged stress and can no longer resist the effects of a stressor, irreversible physiological damage can occur affecting both the brain and the body causing loss of bone minerals, immunosuppression, and changes in the neural circuitry of the hippocampus (McEwen, 2004b; Sapolsky, 1996). Because stress lowers one's resistance, and because repeated stress results in repeated wear and tear on the body in general, the organism facing prolonged bouts of stress is at increased risk for disease.

Psychosocial stress refers to acute or chronic stressors that may be of psychological (internal) or social (external) origin. An acute stressor (e.g., having a near-miss motor vehicle accident) triggers an immediate stress response that usually

subsides shortly after the stressor itself has ceased to exist or is no longer present in the individual's life. On the other hand, a chronic stressor (e.g., ongoing financial problems or a lengthy illness) occurs over a prolonged period of time, where a simple or quick solution is not available (Baum, Cohen, & Hall, 1993). Both acute and chronic stressors may lead to a range of behavioural and physiological impairments (Lupien, McEwen, Gunnar, & Heim, 2009; McEwen, 2004a; McEwen, 2007).

Stress: Its Impact on Cognition

The experience of stress is associated with adverse effects on both physical and mental health. Recent research focus is especially on the effects of excessive stress on human cognition (Lupien et al., 2009; Sandi, 2013). The fields of psychology and medicine have provided strong evidence to support the notion that stress has a negative impact on human cognitive performance, and that this negative impact is aggravated in old age (Stawski et al., 2006; Sterlemann et al., 2010). Additionally, empirical evidence suggests that the negative effects of stress contribute to the development of AD (Peavy et al., 2012; Wang, Wahlberg, Karp, Winblad, & Fratiglioni, 2012).

At this point, there must be a digression to acknowledge the fact that there are numerous risk factors for AD, many of which may interact with one another, further accelerating disease progression (Qiu, 2012; Vagelatos & Eslick, 2013). Thus, this dissertation takes a biopsychosocial approach to understanding the interplay of biological, psychological, and social factors that underlie cognitive functioning, and cognitive decline, in older adults.

More than three decades ago, George Engel (Engel, 1977), an American psychiatrist, suggested that physicians should consider adopting a biopsychosocial model as an alternative to the prevailing biomedical model. The premise underlying this argument was that although the biomedical model played a significant role in identifying physiological and biochemical deficiencies in the body, one could not ignore the considerable influence that biological, psychosocial, and social factors could also have on human functioning in the context of disease and illness. For the purposes of this research, adopting the biopsychosocial approach was appropriate because this study was descriptive and relational. Hence, pursuing a true experimental approach would not have been feasible. It was not my intention to isolate all potential confounding variables in order to examine the influence of one particular variable on an

outcome. Rather, to align my research with the multifactorial nature of AD, I wished to explore the influence of several factors on cognitive functioning and on one another.

Returning from the digression: To my knowledge, there are no studies that have investigated the combination of different types of psychosocial stress, cortisol, apolipoprotein ϵ4, Aβ, hippocampal volume together, considering their relationships with one another and with cognitive function in normal ageing and in AD.

The next section will focus specifically on AD, discussing briefly its epidemiology, pathology, symptoms, course and prognosis, clinical assessment, diagnosis, and treatment. I do not aim to provide an all-encompassing discussion of AD (for such discussion, see works by Ballard et al., (2011); Minati et al., (2009); and Perry et al., (2013)), but rather an introductory overview suited to the scope and constraints of a doctoral dissertation in psychology. The factors in which I am particularly interested, and that are investigated in Study 1, will be discussed in more detail in the *Introduction to Study 1*.

Alzheimer's Disease: A Brief Introduction

AD is the leading cause of dementia worldwide and is the sixth-leading cause of death in high income countries (HIC) (Alzheimer's Association, 2013). DSM-IV-TR criteria specify that the term 'dementia' refers to a memory deficit demonstrated on objective cognitive testing, along with impairment in at least one other cognitive domain (e.g., language, thinking, planning, or reasoning), to such an extent that it interferes with an individual's daily life and activities (American Psychiatric Association, 2003). AD is a progressive, irreversible brain disease that is characterized by a gradual onset, continuing cognitive and functional decline, and personality changes (Braak & Braak, 1995).

The characteristics of AD were first described by a German neurologist and psychiatrist, Alois Alzheimer, in his 1907 paper, "Über eine eigenartige Erkankung der Hirnrinde". In his paper, which was subsequently translated into English, (Alzheimer, Stelzmann, Schnitzlein, & Murtagh, 1995; Strassnig & Ganguli, 2005), Alzheimer documented the case of a 51-year-old woman whom he saw in a psychiatric institution in Frankfurt am Main. The first symptom with which she presented was jealousy of her husband. There followed rapid memory loss, disorientation, misplacing objects, delusions of persecution, and behavioural changes; these symptoms progressed with

time until her death four-and-a-half years later. Following her death, Alzheimer examined her brain and identified abnormal plaques and entangled bundles of fibres. These plaques have since become known as amyloid plaques; the twisted fibres are now called neurofibrillary tangles. The plaques consist largely of Aβ and the tangles of hyperphosphorylated tau protein (Sheng, Sabatini, & Sudhof, 2012).

More than 100 years since that initial description of the disease, AD has a prominent place in scientific research. We now have a far better understanding of the disease process, and neuroscientists are making good headway in understanding the roles different factors may play in the pathogenesis of the disease. That said, however, the cause of AD remains unknown in most cases. (Some rare, inherited forms of the disease are known to be caused by specific mutations in the gene for amyloid precursor protein (APP) on chromosome 21 and the presenilin 1 (PS1) and presenilin 2 (PS2) genes on chromosomes 1 and 14 respectively; (Petrella, Coleman, & Doraiswamy, 2003). There is much that we still do not understand about the sporadic form of the disease, particularly with regard to how certain factors may interact with one another to cause or worsen disease progression, or with regard to which individuals are at the highest risk for developing the disease.

Epidemiology. A recent study using the latest data from the 2010 United States Census and the Chicago Health and Aging Project estimated that 5.2 million Americans of all ages will be living with AD in 2013 (Hebert, Weuve, Scherr, & Evans, 2013). Half of these people may not, because of lack of awareness or access to appropriate healthcare services, even know they have the disease (Alzheimer's Association, 2013).

An earlier Delphi consensus study estimated that the global prevalence of dementia in 2001 was in the region of 24 million people, of which 70% were cases of AD (Ferri et al., 2005). The study noted that that number was predicted to double every 20 years, to 42 million by 2020 and to 81 million by 2040. These estimates were based on the assumptions of no changes in mortality and of no effective preventative or curative strategies. A global increase in numbers of people with dementia will undoubtedly lead to an even more costly burden of disease in the years to come. The Delphi consensus study also estimated that 60% of patients with dementia live in LAMICs, and that the rates of increase in people with dementia will be much higher by 2040 in those countries than in HICs.

It is, however, advisable to interpret the findings regarding LAMICs with caution, as relatively few studies of AD have been performed in these regions.

Nonetheless, data from studies in India, China and southeast Asia, Latin America and the Caribbean, and Africa (Chandra et al., 1998; Mathuranath et al., 2012; Prince et al., 2003; Scazufca et al., 2008; Shaji, Bose, & Verghese, 2005) are fairly reliable. These studies present prevalence and incidence rates of AD and dementia. The three studies performed in regions of India reported prevalence and incidence rates of AD and dementia that were generally lower than those reported for HICs, and the study in Brazil reported a prevalence of dementia similar to that reported for African countries.

Currently, there are no South African epidemiological data regarding AD. However, anecdotal evidence from local memory and geriatric clinics suggests that the presence of AD is not uncommon. (I discuss prevalence studies in Africa towards the end of the *Introduction to Study 1*, under the title *Alzheimer's disease in the South African context*.)

Risk factors. Empirical research has identified numerous risk factors for the development of AD. These risk factors have been identified via either observational studies (such as case-control and cross-sectional studies) or experimental studies (such as clinical trials; (Reitz, Brayne, & Mayeux, 2011)). Advancing age is a risk factor for AD, although AD is not a characteristic of normal ageing. The onset of AD before the age of 60 years is rare and is the result of either a mutation in the gene coding for APP or, more frequently, the PS1 or PS2 genes (Petrella et al., 2003).

Currently, the only other confirmed risk factors for increasing the risk of developing AD include having a first-degree family member with dementia (Green et al., 2002), and presence of the ϵ4 allele of the APOE gene (Lindsay et al., 2002; Notkola et al., 1998; Sando et al., 2008b). Some other potential risk factors that have been identified in the scientific literature include risk factors that increase the possibility of cardiovascular disease such as hypertension, obesity, and high cholesterol (Luchsinger et al., 2005; Reitz et al., 2011); traumatic brain injury (Jellinger, Paulus, Wrocklage, & Litvan, 2001; Sivanandam & Thakur, 2012); psychosocial stress (Alkadhi, 2012; Wang et al., 2012); low levels of education (Evans et al., 1997; Gatz et al., 2001); and lower socioeconomic status (Evans et al., 1997).

MCI has also been shown to be a risk factor for AD (Damian et al., 2013; Levey, Lah, Goldstein, Steenland, & Bliwise, 2006). MCI represents a midway point between healthy cognition and a diagnosis for AD (Petersen, 2011). The original clinical criteria for MCI included concern about a change in cognition, impairment in one or more cognitive domains, normal general cognitive functioning, intact activities

of daily living, and no dementia (Petersen et al., 2001). Some researchers argue that MCI is a prodromal stage of AD (Drago et al., 2011); while others propose that it is a separate entity that may be representing something different, such as microvasculopathy. It has been demonstrated that not all cases of MCI progress to AD; some remain MCI and others may even revert back to healthy cognition (Britt et al., 2011).

Pathology. AD-type pathology is a significant predictor of dementia throughout the lifespan (Dolan et al., 2010). Usually, the pathological process of AD begins in the entorhinal cortex; at this stage, the disease is asymptomatic; i.e. there are no clinical symptoms. The pathology then progresses to the limbic system, including the hippocampus, and spreads further to associated regions of the neocortex (Braak & Braak, 1991). A magnetic resonance imaging (MRI) scan of the brain of a patient with early AD usually shows medial temporal, including hippocampal, atrophy, and enlargement of the temporal horn of the lateral ventricle (Apostolova et al., 2012). The medial temporal structures and temporal poles, as well as the temporoparietal junction, are the brain regions predominantly affected in AD (Frisoni et al., 2005; Harasty, Halliday, Kril, & Code, 1999; Krasuski et al., 1998). The frontal lobes are also involved later in the disease process (Scahill, Schott, Stevens, Rossor, & Fox, 2002).

Microscopically, the hallmark neuropathological characteristics of AD, as seen on histological examination of postmortem brain tissue, include extreme formations of the amyloid plaques and neurofibrillary tangles, as well as eventual atrophy of the temporal, frontal, and parietal lobes. Plaques and tangles appear initially and primarily in hippocampal areas (Serrano-Pozo, Frosch, Masliah, & Hyman, 2011).

The Aβ protein represents a cleaved fragment of the larger molecule, APP. The latter is a normal component of nerve cells (Selkoe, 2003). In the brains of healthy individuals, amyloid protein fragments are broken down and eliminated. In individuals with AD, however, these fragments accumulate, aggregate, and form hard, insoluble plaques in the brain parenchyma. Scientists consider these plaques to be central for neurodegeneration in the disease; this abnormal metabolism of APP is referred to as the "amyloid cascade hypothesis" (Karran, Mercken, & De, 2011).

Neurofibrillary tangles are intracellular insoluble twisted protein fibres located within nerve cells. These fibres consist of a protein called tau that normally occurs in neurones. However, when processed abnormally, as is the case in AD, tau molecules

clump together, become hyperphosphorylated, and form tangles, which lead to neuronal death (Iqbal & Grundke-Iqbal, 2006).

Both neuritic plaques and neurofibrillary tangles which may also be found in smaller amounts in the brains of healthy elderly persons may interfere in some way with normal cellular functioning. One hypothesis regarding this abnormal cellular functioning is that these plaques and tangles may stimulate a neuritic inflammatory response (Wilcock, 2012). The formation and aggregation of plaques and tangles often precede a loss of synaptic connections and neuronal death. However, neuroscientists still debate whether the plaques and tangles are a cause or a consequence of the disease.

Clinical symptoms, course, and prognosis. AD is characterized by a gradual onset and progression of episodic memory impairment that is disproportionate to functioning in other cognitive domains (Salmon & Bondi, 2009). In most cases, common symptoms include misplacing everyday items such as keys and wallets, difficulty keeping track of details such as dates, problems performing multiple and/or complex tasks, and increasing repetitiveness in behaviour and speech.

In the early stages of the disease, patients usually have only a relatively circumscribed cognitive deficit (typically, of episodic memory). With disease progression, cognitive impairment becomes more generalized. Late stages of the disease are often marked by gait disturbances, motor and sensory abnormalities, and seizures. The course of the disease is progressive over several years. A study investigating survival of people with a clinical diagnosis of dementia, including Alzheimer's disease, found that the median survival of people diagnosed at age 60-69 was 6.7 (interquartile range 3.1-10.8) years. This median number decreased to 1.9 (0.7-3.6) years for those diagnosed at age 90 or over (Rait et al., 2010). In the absence of other serious medical conditions, death usually occurs in a state of extreme cognitive impairment, and is often secondary to cardiovascular disease, neoplasms, or complications (e.g., pneumonia or deep vein thrombosis) associated with being immobile and bed-bound (Beard et al., 1996).

Clinical assessment. This assessment usually includes at least a clinical interview and neuropsychological assessment, but ideally includes all four elements described below.

Interview. The clinical history, taken by a healthcare practitioner, plays an integral role in the diagnosis of AD. This history should be obtained from both the patient and a knowledgeable informant who has regular contact with the patient and

who can provide objective collateral information. Using a systematic clinical approach, which includes a thorough interview, assists in defining the diagnosis through collecting pertinent information for creating a future care plan for patients with AD and their families and caregivers (Galasko, Golde, & Scheltens, 2013).

The purpose of the interview is to ascertain information regarding changes in the status of the patient's cognitive, behavioural, mood, and motor functioning, and any recent limitations in their ability to perform activities of daily living. The healthcare practitioner should enquire about the patient's past, particularly with regard to educational and occupational attainment. Other important information that the healthcare practitioner should ascertain as part of the clinical interview includes the patient's current medications and their side effects, alcohol and drug substance intake, symptoms of depression and/or anxiety, appetite and nutrition, sleep disturbance, and pain (Alom, Llinares, & Fajardo, 2012).

Neuropsychological assessment of Alzheimer's disease. Neuropsychological testing plays an important role in the diagnostic assessment of older adults with cognitive impairment in early disease stages (Chapman et al., 2010; McKhann et al., 1984). Neuropsychological testing may be useful for differentiating cognitive changes associated with normal ageing from those associated with a neurodegenerative disease, and it helps to distinguish different types of dementia (Weintraub, Wicklund, & Salmon, 2012). The neuropsychological profile of AD is best recognized in the beginning stages of the disease, when the symptoms relate to the brain regions most affected in early AD (e.g., amnesia with hippocampal involvement). With disease progression and particularly in later disease, distinct neuropsychological profiles are more difficult to discern because of the more widespread and generalised neuroanatomical involvement (Salmon & Bondi, 2009).

Although the neuropsychological presentation of AD may vary across patients, there are certain cognitive symptoms that are almost always present. Frequently, the neuropathology of AD targets, initially, the limbic regions (Serrano-Pozo et al., 2011) involved in episodic memory functioning (i.e., the ability to learn and recall recent information). Hence, pathological changes in this region manifest in the hallmark neuropsychological feature of AD, namely a deficit in episodic memory (Salmon & Bondi, 2009). As the disease and its associated pathology progress, other neocortical regions become affected, resulting in additional cognitive symptoms. These symptoms

often include deficits in language, semantic knowledge, visuospatial abilities, executive functioning, attention, working memory, and praxis (Weintraub et al., 2012).

Although the focus of early cognitive deficits in AD has largely fallen on episodic memory (Gold & Budson, 2008), a recent meta-analysis proposes that a predominantly nonspecific cognitive decline can also occur prior to a diagnosis of dementia, during a preclinical phase (Backman, Jones, Berger, Laukka, & Small, 2005). Even though a decline in episodic memory functioning is the most common feature of AD in the early stage of the disease, studies have also demonstrated deficits in the domains of executive functioning, visuospatial ability, perceptual speed, attention, and verbal skills (Backman & Small, 2007). This decline in cognitive functioning across a variety of domains provides support for the notion that several brain regions (including the medial temporal lobes, frontal lobes, and anterior cingulate gyrus) are impaired in preclinical AD (Small, Mobly, Laukka, Jones, & Backman, 2003).

Laboratory studies. It is standard practice where dementia is considered a possible diagnosis to perform routine blood tests to identify possible systemic factors. Cognitive impairment can sometimes be caused by a vitamin B12 deficiency, thiamine deficiency, or hypothyroidism. Additionally, metabolic problems such as diabetes (Xu, von, Qiu, Winblad, & Fratiglioni, 2009) and hyperinsulinemia (Luchsinger, Tang, Shea, & Mayeux, 2004) should be investigated because they can affect the progression of AD and are associated with concomitant cerebrovascular disease. Hyperlipidemia has also been proposed as a possible risk factor for AD, but empirical evidence is controversial and the relationship between cholesterol and AD remains unclear (Chui, Zheng, Reed, Vinters, & Mack, 2012)**.**

Neuroimaging. Structural neuroimaging scans such as computed tomography (CT) or MRI can be useful additional tests for excluding other possible causes of cognitive impairment (e.g., brain tumours, stroke, or subdural haemorrhage). In AD, structural MRI may demonstrate widespread cortical and hippocampal atrophy with ventricular enlargement (Frisoni, Fox, Jack, Jr., Scheltens, & Thompson, 2010). For instance, Moghekar and colleagues (2012) reported that MRI-detected cerebral white matter disease was associated with AD-type brain pathology at autopsy in a sample of 50 participants from the Baltimore Longitudinal Study of Aging Autopsy Program. These researchers proposed that this relationship may explain, at least partly, the association between cerebral white matter disease and cognitive decline in older adults. In some cases, the use of cerebral perfusion single photon emission computed

tomography scans may also aid diagnosis of AD (Matsuda, 2007; O'Brien, 2007; Soonawala et al., 2002).

Diagnosis. As detailed above, the diagnosis of AD is dependent on a detailed history from the patient and his or her relative or informant, including an account of previous and current level of functioning, a physical examination, cognitive testing, blood tests, and neuroimaging. Of all these factors, the most important one is to obtain a reliable history of the illness, including time of onset and nature of the progression (Ropper & Brown, 2005).

Based on the results from these different methods of investigation, the diagnosis is largely made by exclusion of other causes of progressive dementia. Probable AD, following the NINCDS/ADRDA criteria, is defined by deficits in at least two areas of cognitive ability, including memory, in an individual demonstrating progressive deterioration, whose activities of daily living are also significantly impaired and where there is no evidence of an alternative cause for the symptoms (McKhann et al., 1984).

The NINCDS/ADRDA (McKhann et al., 1984) and the DSM-IV-TR (American Psychiatric Association, 2003) criteria for the clinical diagnosis of possible or probable AD include progressive memory impairment, and one (or more) of the following cognitive disturbances: aphasia (language problems), apraxia (decline in ability to perform learned, purposeful movements), agnosia (inability to identify objects despite operational sensory function), disturbances in executive functioning (i.e., difficulty with planning, organizing, sequencing, problem-solving, and/or abstract reasoning), and perceptual difficulties. To meet diagnostic criteria, these memory impairments and other cognitive disturbances must produce major difficulties in social or occupational functioning, and must also represent a considerable decline from a previous level of functioning. Other clinical features that contribute to a diagnosis of probable AD after excluding other causes of dementia include neurological abnormalities such as increased muscle tone and a shuffling gait (McKhann et al., 1984). Patients with AD are also known to have a high prevalence of non-cognitive symptoms (Fernandez, Gobartt, & Balana, 2010); thus, the diagnosing healthcare professional should also enquire about the presence of affective and behavioural symptoms such as depression, insomnia, incontinence, delusions, hallucinations, weight loss, sex problems, and substantial verbal, emotional, and physical outbursts.

From experience acquired recently by clinicians and researchers, it has emerged that often the diagnosis of AD can be identified in a prodromal phase, as the

pathophysiological process of AD is thought to commence years prior to diagnosis (Sperling et al., 2011). With this experience in mind, there have been several reviews of the NINCDS/ADRDA criteria (Dubois et al., 2007). The National Institute on Aging and the Alzheimer's Association assembled an international workgroup to evaluate the currently available biomarker, epidemiological, and neuropsychological data. This group was also tasked with forming recommendations to identify factors that predict most strongly the risk of progression from "normal" cognition to MCI (Petersen, 2004; Petersen, 2011) and AD. The workgroup compiled two sets of criteria (Albert et al., 2011); the first set is core clinical criteria that could be used by healthcare providers without access to advanced imaging techniques or cerebrospinal fluid (CSF) analysis. The second set of criteria integrates the use of biomarkers based on imaging and CSF measures. Currently, these recommendations are exclusively intended for the purposes of research and do not have any clinical applications. However, the aim is to validate the criteria that use biomarkers and to standardize biomarker analysis for clinical use in community settings (Albert et al., 2011).

Differential diagnosis. When an older adult presents with cognitive change, AD is a possible diagnosis and can be determined fairly accurately based on the aforementioned criteria (Braaten, Parsons, McCue, Sellers, & Burns, 2006). In some cases, however, patients may present with unexpected or additional clinical features; this situation raises the possibility of other differential diagnoses or AD combined with other conditions. Clinical symptoms can also overlap in the presentation of different dementias such as AD, fronto-temporal dementia, and vascular dementia.

Cerebrovascular disease often accompanies AD; its presence is known to increase the burden of AD, and can also affect the clinical expression of AD (Helzner et al., 2009). Vascular risk factors are known to have negative effects on the brain and cognitive functioning (O'Brien et al., 2003). Consideration of vascular risk factors is particularly relevant in South Africa and other LAMICs, as populations of these countries frequently show high levels of hypertension, cholesterol, and diabetes mellitus, in conjunction with poorer nutrition and less access to healthcare resources. Additionally, in South Africa one must consider the effect of infection on cognitive functioning because rates of systemic infection, primarily arising from HIV/AIDS, are high.

Treatment. Currently, there is no cure for AD and treatment is symptomatic, i.e. it only treats the symptoms and not the cause. Both pharmacologic and non-pharmacologic interventions are available, but neither prevents or cures the disease.

Over the past two decades, the main pharmacologic treatments for AD have targeted the brain's underlying deficiency of acetylcholine. Acetylcholinesterase inhibitors raise brain levels of acetylcholine by blocking the enzyme responsible for its degradation. These drugs, namely donepezil, rivastigmine, and galantamine, are used for specific symptomatic treatment of cognition and behaviour in mild to moderate AD (Birks & Harvey, 2006). A systematic review and meta-analysis of placebo-controlled data support these drugs' modest overall benefits for stabilizing or slowing decline in cognition, function, behaviour, and clinical global change (Hansen et al., 2008). However, although cognitive function may improve and remain above the pre-treatment baseline for the first year, it subsequently declines. Memantine, a drug labelled for moderate to severe AD, operates via a different mechanism of action; it regulates the effects of the neurotransmitter glutamate and can slow the progression of symptoms. Reportedly, this drug benefits cognitive, ADL, and global functioning (Rainer et al., 2011; Schmitt & Wichems, 2006).

Non-pharmacologic interventions aim to address behavioural and psychiatric symptoms of the disease (Gauthier et al., 2010). These interventions include, for example, simplifying tasks, reducing excess stimulation, and adapting the caregiving environment, with a focus on person-centered care (Brooker, 2003).

Conclusion

The actual cause of cognitive impairment and AD is unknown, but research suggests that several factors may be responsible and that these factors may act synergistically to precipitate or accelerate its progression. Thus, an approach exploring a range of factors associated with cognitive functioning in a multi-disciplinary way is both logical and necessary. Both the cross-sectional and longitudinal studies reported in this dissertation aim to explore cognitive functioning and AD in South African older adults. They also aim to contribute new knowledge about such associations in a LAMIC in which age-related diseases are largely ignored. Improved knowledge and factors related to cognitive functioning in older adults is particularly relevant for those factors that appear to be modifiable, to a certain degree (e.g., vascular or stress-related risk

factors). Understanding the contributory role of such factors in the development and progression of cognitive impairment may pave the way for future preventative and treatment strategies.

CHAPTER TWO: STUDY 1 – A CROSS-SECTIONAL STUDY

Introduction

Factors Associated with Changes in Cognitive Functioning

The purpose of this introductory section is to provide an overview of the major factors associated with the presence of age-related changes in cognitive functioning. These are factors that have been identified previously as risk factors for the development of AD. This section will not provide an exhaustive review of all risk factors associated with Alzheimer's disease. Rather, it will discuss the risk factors for AD, previously identified as such by prior studies, which were the focus of the current research. Important to note is that the focus of this study is not on risk factors for AD. Rather, these factors are explored in relation to cognitive functioning and as such they were selected because of their association with and risk for the development of AD, and therefore their contribution to cognitive impairment.

This chapter provides a brief review of recent literature on physiological, psychosocial, and sociodemographic factors that have been found to be associated with the presence of AD. Specifically, the physiological factors include changes in the hypothalamic-pituitary-adrenal (HPA) axis functioning, the APOE-ϵ4 allele, Aβ, and hippocampal volume. The psychosocial factors include traumatic life experiences, perceived psychosocial stress, and resilience. The sociodemographic factors include age, sex, and education. All of these factors may be grouped together as affecting, and being affected by, the experience of stress; hence, one might regard stress as the overarching factor of interest in the current research. Below, I discuss each of these factors in terms of their relationships with cognitive functioning and with AD, as well as their associations with the general concept of stress.

Although various studies may refer to risk factors for the development of AD, it is important to note that the term "risk factors" does not necessarily imply causation. Instead, the term implies that a particular variable is associated with increased likelihood of disease occurrence. Additionally, in cross-sectional studies, association does not necessarily imply causation, as the symptoms may be a consequence of the disease itself and may not have preceded the disease at all.

Physiological factors. The physiological factors of interest in this study include changes in HPA-axis functioning, APOE-ϵ4 carrier status, Aβ, and hippocampal volume. Each of these is discussed below in terms of their relationship to cognitive functioning, AD, and stress.

Changes in HPA-axis functioning. When humans are exposed to stressors of any kind, the body responds via two major effector systems, namely the HPA system and the locus-coeruleus-norepinephrine/sympathetic nervous system. These two systems work together and connect the brain with the periphery (Tsigos & Chrousos, 2002). Activation of the latter leads to stimulation of the sympathetic nervous system which prepares the body for the classic "fight or flight" response which was first described by Cannon (1932). Such preparation includes, for example, increasing the availability of glucose and oxygen delivered to the muscles and brain, increasing heart rate and blood pressure, and vasoconstriction (Romero & Butler, 2007).

However, the stress response system of interest in this study is the HPA axis. The HPA axis responds to stress by activating a neuroendocrine response (see Figure 1) and is a key intermediary of the effects of stress on the brain and behaviour. Activity in this system is associated with a range of hormonal, neurochemical, and physiological alterations (Foley & Kirschbaum, 2010). Activation of the HPA axis system after encountering a stressor enables the organism to adapt to increased demands and to sustain homeostasis after a stressful event (Kudielka & Kirschbaum, 2005).

When an individual experiences a stressor, the HPA axis reacts via a series of physiological events; these are depicted in Figure 1. With the occurrence of a stressor, the hypothalamus is triggered to secrete corticotrophin-releasing hormone (CRH); the latter stimulates the anterior pituitary to produce adrenocorticotrophic hormone (ACTH), which, in turn, stimulates the adrenal cortex to release glucocorticoids into the bloodstream (Dickerson & Kemeny, 2004).

The principal human glucocorticoid is cortisol. The release of this hormone is the best characterized marker of the HPA axis response to psychosocial stress. Cortisol is regulated by a negative feedback system (Tasker & Herman, 2011). In this system, high circulating glucocorticoids down-regulate the ACTH and CRH secretions from the pituitary and hypothalamus respectively (Lachize et al., 2009). As part of the acute stress effect, glucocorticoids interact with corticosteroid receptors located throughout the brain; these regulate gene transcription and cellular function subsequent to the impact of the acute stress effects (Phuc et al., 2005).

The hippocampus is a site for two types of corticosteroid receptors, Type I (mineralocorticoid receptors) and Type II (glucocorticoid receptors) (Webster, Knable, O'Grady, Orthmann, & Weickert, 2002). Both types of receptors are also abundant in the amygdala and in the prefrontal cortex (de Kloet, Datson, Revsin, Champagne, & Oitzl, 2008; Sanchez, Young, Plotsky, & Insel, 2000). These receptors are responsible for moderating the neural circuits and neuroendocrine systems that initiate behavioural responses to stress (Russo, Murrough, Han, Charney, & Nestler, 2012). Glucocorticoid receptors have been implicated in both short- and long-term neurobiological adaptations found in response to stressors (Maletic et al., 2007). For example, early-life environmental circumstances permanently alter (a) the development of glucocorticoid expression in the hippocampus, and (b) HPA-axis responses to chronic stress (Weaver, Diorio, Seckl, Szyf, & Meaney, 2004). Glucocorticoids can affect the hippocampus in several ways: They can diminish the excitability of some hippocampal neurones, they can initiate atrophy of dendritic branches in pyramidal cells within the CA3 area, and they can reduce the growth of new neurones in the dentate gyrus (McEwen & Sapolsky, 1995).

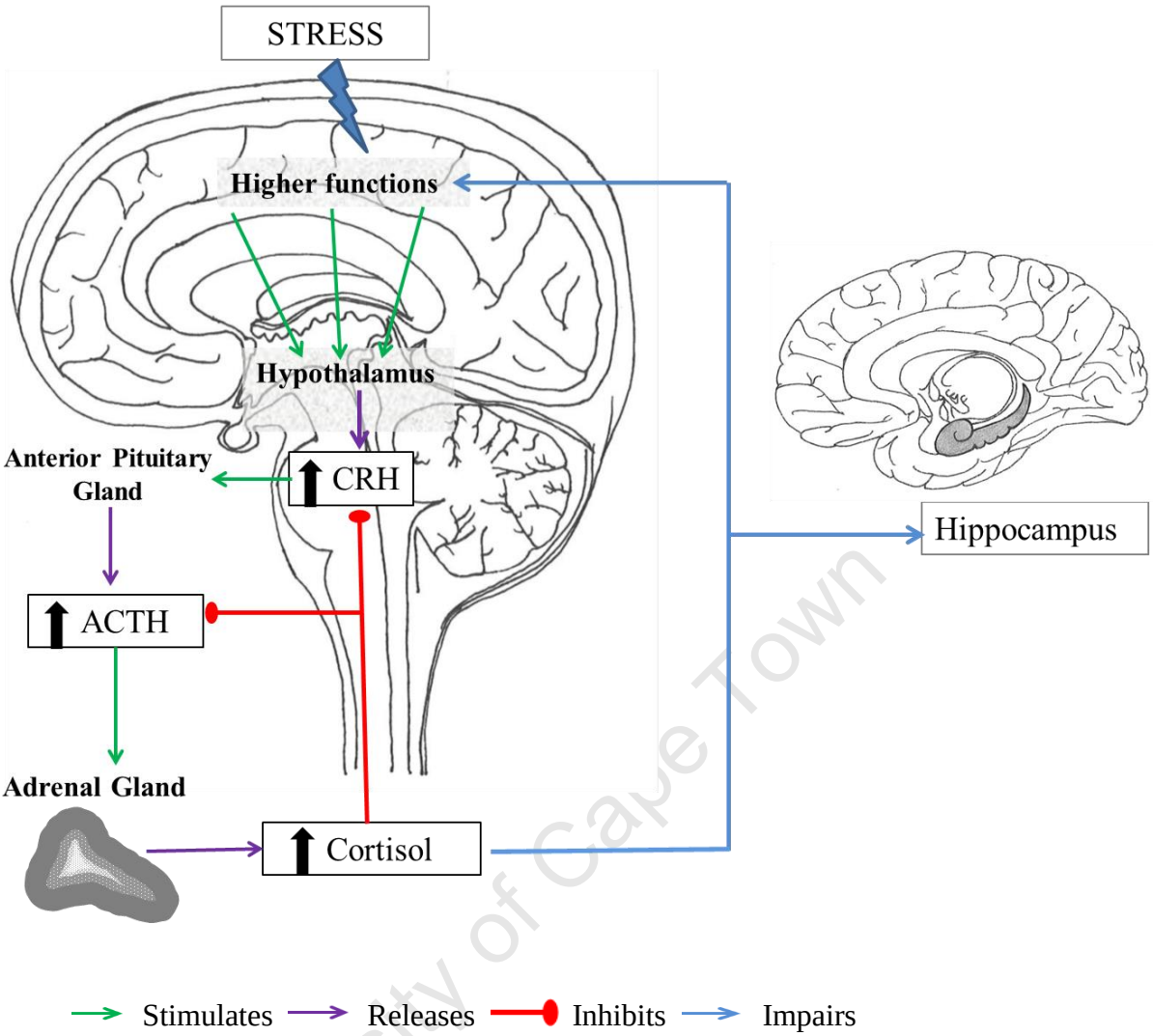


Figure 1. The negative feedback loop of the HPA axis. CRH = corticotrophin-releasing hormone. ACTH = adrenocorticotrophic hormone. The body experiences a stressor; this triggers the hypothalamus to release CRH, which stimulates the anterior lobe of the pituitary gland to release ACTH. The adrenal cortex of the adrenal glands responds to stimulation by the ACTH and produces cortisol. Cortisol has a negative feedback on the hypothalamus and the pituitary gland, inhibiting CRH and ACTH secretion.

Glucocorticoids aid the body in preparing for survival during stressful situations; for instance, they play a role in altering heart rate, blood pressure, and muscle tone. However, if exceptionally high or low quantities of glucocorticoids are released, cognitive and neural processes may be impaired (Welberg, 2009). Findings from animal studies indicate that prolonged stress is associated with elevated glucocorticoid levels and, consequently, with enduring effects on certain brain circuits and systems (McEwen & Sapolsky, 1995). There is general consensus that exposure to stress can cause and/or exaggerate several diseases. For example, in humans, sustained

elevated levels of cortisol have been linked to a variety of medical and psychiatric conditions including hypertension, abdominal adiposity, hyperglycaemia, insulin resistance, dyslipidaemia, and depression (Epel, Lapidus, McEwen, & Brownell, 2001; Herbert, 2013; Whitworth, Williamson, Mangos, & Kelly, 2005). A proposed mechanism behind the harmful effect of stress is that HPA-axis functioning is a marker of allostatic load. A high allostatic load might arise from prolonged overactivation of the stress system (Juster et al., 2010; McEwen, 1998; McEwen & Stellar, 1993).

The effects of chronic stress can therefore accumulate over the course of a lifetime, and may represent a risk factor for cognitive decline and for AD. If individuals experience chronic stress, then they are constantly releasing cortisol. This effect is exacerbated in older adults, whose biological systems become dysregulated and are not shut off as effectively as in young adults (Goldman, Glei, Seplaki, Liu, & Weinstein, 2005; Gouin, Hantsoo, & Kiecolt-Glaser, 2008). Thus, in ageing, cortisol levels increase and are sustained at higher levels for a longer period of time.

Peavy et al. (2007) explored the effects of chronic elevations in cortisol associated with prolonged stress, and found an association with a decline in memory performance. In their study of 91 non-demented elderly participants, they found that those individuals with high stress as a result of recent life events demonstrated higher cortisol concentrations and poorer memory performance than those with low stress.

Elevated levels of circulating cortisol are not only associated with the development of cognitive impairment; they may also play a role in the progression of AD. For instance, Csernansky et al. (2006) assessed, on an annual basis for up to 4 years, 33 subjects with very mild Alzheimer-type dementia and 21 subjects without dementia. They found that higher plasma cortisol levels were related to faster disease progression in AD patients. Consistent with these findings, Bemelmans et al., (2007) showed that plasma cortisol was (a) negatively correlated with concerted retrieval efforts during memory tasks, and (b) positively associated with AD progression. Furthermore, Lupien et al. (1998) detected a direct and significant relationship between elevated cortisol levels, hippocampal shrinkage, and hippocampal-based memory deficits in older adults. I shall discuss the hippocampus, its role in AD, and its link to stress, in more detail later on in this chapter.

Genetics and apolipopoprotein E. As noted previously, there may be a genetic predisposition to developing AD (Farrer et al., 1997). A large twin study (Gatz et al., 2006) using the Swedish Twin Registry provides support for the role of genes in the

development of AD. The study involved 11 884 twin pairs aged 65 years or older, among whom were 392 pairs in which one or both members had AD. Results from this study suggested that heritability for AD is high (reported at 58%) and that the same genetic factors were influential for both men and women. High rates of heritability for cognitive impairment have also been confirmed in a sample of African-Americans. Whitfield, Kiddoe, Gamaldo, Andel, and Edwards (2009) determined concordance rates and heritability for cognitive impairment in 95 same-sexed pairs of older African-American twins from the Carolina African-American Twin Study of Aging. They demonstrated that the heritability for cognitive impairment in their sample was 54%, a number comparable to that reported for the European sample studied by Gatz and colleagues (2006).

One gene that has been strongly linked with the development of AD, and more generally with some aspects of cognitive decline in elderly cohorts, is apolipoprotein E, and, more particularly, its ϵ4 allele. Apolipoprotein E is a protein that is involved in lipid transport and metabolism. It is produced and secreted in the brain and plays a role in neuronal regeneration (Hankey & Wardlaw, 2008). The apolipoprotein E phenotype is coded by a gene that has three common allelic variants: ϵ2, ϵ3, ϵ4 (Geda et al., 2006; Podewils et al., 2005).[1] Corder and colleagues (Corder et al., 1993) studied 42 late-onset AD families in which all individuals were over the age of 60 years. They found that individuals with two ϵ4 alleles had an increased risk for AD, and an earlier age of onset, compared to individuals with one inherited ϵ4 allele. Furthermore, in a study of 218 AD patients, Martins, Oulhaj, de Jager, and Williams (2005) found that APOE genotype strongly predicted rate of cognitive decline; they reported a dose-response relation with the APOE-ϵ4 allele. In North America and Europe, approximately 40-50% of AD patients are APOE-ϵ4 carriers. These patients developed the disease earlier and experienced more rapid progression than AD patients with other APOE allelic variants (Bu, 2009).

Several other studies have investigated associations between APOE-ϵ4 and cognitive functioning. A meta-analysis of 38 studies demonstrated that elderly individuals who possessed at least one APOE-ϵ4 allele performed more poorly than those without an ϵ4 allele on assessments of global cognitive functioning, executive

[1]Interestingly, the ϵ2 allelic variant has been proposed as having a protective effect against the development of dementia (Berlau, Corrada, Head, & Kawas, 2009; Farrer et al., 1997). It is beyond the scope of this project to investigate this particular allelic variant, however.

functioning, and memory (Small, Rosnick, Fratiglioni, & Backman, 2004). Furthermore, Tschanz et al. (2006) found that individuals with MCI had an increased risk of dementia at follow-up after 3 years compared to those without cognitive impairment, and that this risk was further elevated in individuals with the ϵ4 allele compared to those without ϵ4.

In the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) study, Packard et al. (2007) found that a cohort of older APOE-ϵ4 carriers had poorer memory performance and slower information processing over a mean 3.2 year follow-up, compared with APOE-ϵ4 non-carriers. In addition, memory scores decreased 2.5% from baseline in those without ϵ4, 4.3% in ϵ4 heterozygotes, and 8.9-13.8% in ϵ4 homozygotes.

Although most studies of APOE-ϵ4 and ageing have focused on its negative impact on cognition, research studies have investigated whether the presence of this allele in healthy, non-demented controls maintains high cognitive function. Riley et al. (2000) explored this question using a group of 241 female participants with high cognitive functioning, aged 75-98 years, from the Nun Study. This is a longitudinal study of ageing and AD in Catholic nuns. Of the 241 participants who were cognitively intact at the first examination, 65% of those without an ϵ4 allele remained cognitively intact for the duration of their involvement in the study, compared with 41% of those who were ϵ4 carriers. The authors suggested that the absence of the APOE-ϵ4 allele may be related to maintaining high levels of cognitive function in cognitively intact, very old adults. These results, however, appear to contradict previous findings, such as those from the PROSPER study.

The studies discussed above, and investigations into the effect of the APOE-ϵ4 allele on cognitive performance in patients with probable AD, have primarily been performed on populations of European descent from the global north (and the Western hemisphere, in particular). Hua and colleagues (2008) reported that within these groups, the APOE genotype frequencies of ϵ3/ϵ4 and ϵ4/ϵ4 were 21.2% and 2.8% respectively, in healthy controls. In AD patients from the same population group, the APOE genotype frequencies of ϵ3/ϵ4 and ϵ4/ϵ4 were 44.2% and 19.9%, respectively.

The prevalence of APOE-ϵ4 and its influence on the development of AD in LAMICs, and in ethnic minority populations in developed countries, remains unclear, with conflicting reports indicating either little or no increase in AD in the presence of the allele (Evans et al., 2003). Although scarce, there is some research investigating AD

in African populations. For example, Sepehrnia and colleagues (Sepehrnia, et al., 1989) reported that the APOE-ϵ4 allelic frequency in a sample of non-demented Nigerian adults was 30%. Similarly, in a group of elderly Kenyan participants, Sayi et al. (1997) found comparable frequencies of the APOE-ϵ4 allele (25%), with no clear difference in frequency between demented and non-demented subjects. Based on their preliminary observations, the authors suggested that elderly East Africans with no obvious clinical AD possessed relatively high APOE-ϵ4 allelic frequencies compared to healthy ageing participants from Western countries, including African-Americans. In support of the notion that people of African descent possess high frequencies of APOE-ϵ4, Sandholzer, Delport, Vermaak, and Utermann (1995) reported a high allelic frequency of APOE-ϵ4 (0.37), in a South African Khoi San sample. This frequency is twice as high as that found in control populations of European descent reported in other studies (Farrer et al., 1997; Sando et al., 2008b).

Focusing on individuals of African ancestry, the Indianapolis-Ibadan Dementia Study explored the association between APOE genotype and the risk for AD (Gureje et al., 2006; Hendrie et al., 1995; Sahota et al., 1997). This longitudinal, cross-cultural study of AD featured African-Americans residing in Indianapolis, Indiana, and Yoruba residing in Ibadan, Nigeria. The researchers studied these two populations because they are of related ethnic origin, a consequence arising from the slave trade commencing in the 16th century, where some West Africans were forced to migrate to the Americas and West Indies (Bennett et al., 2003). Although the populations from Indianapolis and Ibadan may share genetic similarities, they have different environmental and cultural contexts. This situation provided a unique opportunity to study possible interactions between genetic and environmental factors (Hendrie et al., 1995). Results from these studies indicated that APOE-ϵ4 was associated with an increased risk for AD in the African-American sample (Hendrie et al., 1995; Murrell et al., 2006; Sahota et al., 1997). However, this association was not found in the Nigerian sample, despite APOE-ϵ4 allelic frequencies similar to those in African-Americans (Gureje et al., 2006).

This disparity confirmed findings from an earlier study of elderly Nigerians, which also reported a lack of an association between APOE-ϵ4 and AD (Osuntokun et al., 1995). That study reported an APOE-ϵ4 allelic frequency of 16.7% in AD patients compared with 20.5% in the control subjects. Further confirming the lack of association between APOE-ϵ4 and AD, (Gureje et al., 2006) a recent study conducted in older adults from rural Benin found no adverse effect of APOE-ϵ4 on the risk of cognitive

impairment and dementia (Guerchet et al., 2009). Furthermore, the frequency of APOE-ϵ4 in that sample was high, at approximately 20%, and consistent with the APOE-ϵ4 allelic average in Africa, which is about 20.9%.

Given the reported high frequency of APOE-ϵ4 in some African samples, yet the lack of association between APOE-ϵ4 and AD found in some African studies, it is plausible to question whether, in African populations, the influence of APOE-ϵ4 on cognitive functioning is mediated by other genetic or environmental factors (Reser, 2009). One such mediating factor might be dietary lipid intake, which may play a role especially in increasing the effect of APOE-ϵ4 on cognitive functioning in the more industrialized urban populations, such as the Indianapolis African-Americans mentioned above (Petot et al., 2003; Carvalho-Wells, Jackson, Lockyer, Lovegrove, & Minihane 2012; Florent-Bechard et al., 2009; Hall et al., 2006). There is broad genetic and cultural diversity in African populations; therefore, it should not be surprising that the relationship between APOE-ϵ4 and cognition varies across different African samples.

Research suggests that an interaction between psychosocial factors and APOE-ϵ4 may have an effect on general health and wellbeing. For instance, Hakansson et al. (2009) explored the association between mid-life marital status and cognitive function in later life, with special focus on APOE-ϵ4. With an average follow-up of 21 years, they found an increased risk for AD in individuals who lost their partner before mid-life and were still widowed or divorced at follow-up; this risk was further increased in carriers of the ϵ4 allele. Similarly, exploring the combined influence of psychosocial stress and genetic factors on health, Zeng and colleagues (Zeng, Hughes, Lewis, Li, & Zhang, 2011) reported that interactions between the APOE-ϵ4 allele and one of four life-stress factors significantly increased the odds ratio of poor self-reported health. These life-stress factors included being a relocated mainlander (individuals who were forced to leave mainland China for Taiwan) in China, living in a crowded household with six or more persons, living in an earthquake-damaged house, and monthly financial difficulty. These factors had a substantially larger adverse impact on self-reported health in APOE-ϵ4 allele carriers than in non-carriers.

Based on findings such as these, researchers have proposed that the pathological process of AD may be initiated by gene-environment interactions. Peavy et al. (2007) examined the interaction between an environmental factor (i.e., "real-life" stress, as opposed to experimentally-induced stress; for instance, hospitalization) and a genetic

risk factor for AD (i.e., the ϵ4 allele) in explaining cognitive performance in a sample of 91 non-demented older adults (mean age: 78.8 years). Low-stress participants demonstrated better cognitive performance than high-stress participants on tests of delayed recall, list learning, and immediate and delayed recall of visual designs. Participants without the ϵ4 allele obtained better scores than participants with ϵ4 on tests of immediate and delayed recall of visual designs. The authors also reported significant stress by APOE-ϵ4 interaction effects on memory and cortisol in the high-stress, ϵ4-positive group. Participants in this group displayed consistently poorer memory performance compared to the high stress, ϵ4-negative group, the low-stress, ϵ4-positive group, and the low-stress, ϵ4-negative group. Participants in this group also had higher cortisol levels than those in the low-stress, ϵ4-positive group; cortisol levels did not differ in the high- and low-stress groups who were ϵ4-negative.

Similarly, Lee et al. (2008) investigated APOE-ϵ4 carrier status, cortisol levels, and cognitive function in community-dwelling older adults. Their results showed that, even though a higher cortisol level was associated with lower cognitive scores, the slopes of the adverse relations were steeper in individuals with at least one APOE-ϵ4 allele. The authors suggested that cortisol's relationship with cognitive functioning is modified by APOE-ϵ4, such that the ϵ4 allele increases the vulnerability of the ageing brain to the negative effects of stress.

Beta-amyloid and the amyloid hypothesis. Although it is generally accepted that, in most cases, late-onset AD has a multifactorial etiology, the amyloid cascade hypothesis is a widely accepted mechanistic explanation for the development of AD pathology. It proposes that in both autosomal dominant AD, associated with APP mutations, PS1, and PS2, and in sporadic AD, Aβ accumulation in the brain plays a central role in AD pathophysiology. Furthermore, the ensuing disease process, including the formation of neurofibrillary tangles, results from an imbalance between Aβ production and Aβ clearance (Crews & Masliah, 2010; Hardy & Selkoe, 2002; Holtzman, Herz, & Bu, 2012).

Much of what we know about Aβ in AD comes from transgenic mouse models. In these studies, the mutant human APP genes that cause familial AD have been inserted into mice so that they exhibit some of the pathological features of AD. These mice can then be studied with respect to the accumulation of insoluble Aβ, alpha-synuclein, and neuronal deficits (see, e.g., Gallardo, Schlüter, Südhof, 2008; Masliah et al., 2001).

The presence and accumulation of Aβ-containing neuritic plaques in conjunction with neurofibrillary tangles are the pathological hallmarks of Alzheimer's disease (Verbeek, Eikelenboom, & de Waal, 1997). Aβ plaques develop in the extracellular spaces and neurofibrillary tangles form inside nerve cells. The formation of these amyloid plaques and neurofibrillary tangles appear to contribute to the degeneration of brain neurones and the ensuing symptoms of AD (Caughey & Lansbury, 2003). Both the Aβ plaques and NFTs are accompanied by brain inflammation and neuronal loss (Iqbal & Grundke-Iqbal, 2006).

Neuritic plaques are predominantly composed of collections of 42/43 amino acid β-amyloid peptides (Takahashi, Nam, Edgar, & Gouras, 2002). Beta-amyloid, a peptide of 39-43 amino acids, is formed after cleavage of the APP; the latter is a long trans-membrane protein consisting of 771 amino acids. The proteolytic action of two enzymes (beta-secretase and gamma-secretase) cleaves APP to produce Aβ (Haass, Kaether, Thinakaran, & Sisodia, 2012). The predominant lengths of the Aβ peptide are β1-40 (Aβ1-40) and β1-42 (Aβ1-42). Where the role of beta-secretase is altered, there is increased production of Aβ42 (Holtzman, 2009). The 42-length amino acid is chemically "stickier" than the other lengths, thus increasing its likelihood of clumping together to form plaques. Aβ42 is highly concentrated in neuritic plaques, and its accumulation is proposed as a common mechanism underlying all types of AD (Roher et al., 1993). Within this theoretical framework, Aβ activates the resident inflammatory macrophages of the brain, the microglial cells. These activated microglia secrete neurotoxic inflammatory mediators, which then damage the neurones. Recent murine work has shown that a microglia-mediated inflammatory process in the hypothalamus drives ageing, leading to shortened lifespan and impaired cognition (Zhang et al., 2013). The neuronal loss in humans that occurs in AD may therefore largely be the result of secondary inflammatory responses to Aβ deposition (Sondag, Dhawan, & Combs, 2009).

Stress has been investigated in murine studies in relation to Aβ. In a recent review, Dong and Csernansky (2009) summarized the effects of stress and stress hormones on Aβ and on plaque deposition. Specifically, they examined the relationships between chronic stressors, on the one hand, and HPA-axis activity, Aβ protein, and Aβ plaque deposition, on the other, in mouse models of AD. They suggested that physical and psychosocial stressors acting on the HPA axis influenced the pathogenesis of AD. Stress increased levels of brain corticotrophin-releasing factor

(CRF). In turn, the increased presence of CRF led to increased neuronal activity, Aβ release, and finally, amyloid aggregation into plaques.

As an empirical demonstration of this process, Carroll et al. (2011) studied restraint/isolation-induced stress in a model of chronic stress that exacerbated Aβ accumulation in transgenic (Tg) mice with an APP mutation (Tg2576). They then extended this stress paradigm to a tau transgenic mouse model with the P301S mutation (PS19). In the Tg2576 mice, one month of restraint/isolation stress increased Aβ levels, suppressed microglial activation, and impaired spatial and fear memory, compared with non-stressed mice. One month of restraint/isolation stress in the PS19 mice increased tau hyperphosphorylation, insoluble tau aggression, neurodegeneration, and fear-memory impairments. The combination of these results suggests that prolonged stress, through dysregulation of the HPA axis, increases Aβ production and deposition, as well as tau phosphorylation. Thus, prolonged stress may contribute to the neuropathogenesis of AD.

In further support of this idea, Green, Billings, Roozendaal, McGaugh, & LaFerla (2006), using *in vitro* and *in vivo* murine experiments, found that stress-level glucocorticoid administration increased Aβ formation by increasing steady-state levels of APP and beta-site APP cleaving enzyme 1 (BACE1). These authors also found that glucocorticoids enhanced tau accumulation, implying that these hormones played a role in accelerating the development of neurofibrillary tangles. These findings suggest that high levels of glucocorticoids, associated with AD, may not only be a consequence of the disease process but may also play a central role in its development and progression.

To date, most investigations of Aβ in humans have mostly involved measuring Aβ levels in CSF samples. Recently, however, positron emission tomography (PET), using Pittsburgh Compound-B-C11 as a radiotracer that binds to Aβ plaques, has been used to measure plaque burden in the brain (Wolk et al., 2012). Both of these methods, however, are invasive (in the case of CSF sampling) and costly (in the case of PET imaging). Hence, there is a need to identify biomarkers in measurable samples that are easier and cheaper to obtain (e.g., blood samples). One such blood-based biomarker that has received increasing attention as a potential diagnostic marker is plasma Aβ.

Aβ is a solute that is thought to be cleared from the brain via the CSF-brain barrier into the CSF and then into the venous drainage system of the brain (Toledo, Shaw, & Trojanowski, 2013). However, plasma Aβ measurements are more prone to variability than CSF, and attempts to relate plasma Aβ levels to the diagnosis of AD

have produced contradictory results (Rissman, Trojanowski, Shaw, & Aisen, 2012). Some of the difficulties may arise through inter-assay variation. Recent work by Figurski et al. (2012), however, using improved standardized protocols for the measurement of plasma Aβ, has found significant correlations between plasma Aβ and CSF biomarkers. For example, they reported that plasma Aβ1-42 was negatively correlated to the following: CSF phosphorylated tau 181 (p-tau), CSF p-tau 181/Aβ1-42 ratio, CSF tau/Aβ1-42 ratio, CSF tau, and CSF Aβ1-42. These authors noted, though, that the observed correlations were not strong enough to support the use of plasma Aβ as diagnostic tool, but that Aβ1-42 could be used as a pharmacodynamic marker for drug trials of amyloid-modifying therapies.

Studies have explored the independent roles of the Aβ1-40 and Aβ1-42 peptides, and the role of the relative proportions of these two peptides (i.e. the Aβ1-42/Aβ1-40 ratio), in sporadic AD. Koyama et al. (2012) conducted a systematic review and meta-analysis of studies investigating whether plasma Aβ levels predicted the development of dementia, AD, and cognitive decline. They concluded that lower ratios of plasma Aβ1-42/Aβ1-40, in general, predict the development of AD, but that Aβ1-42 and Aβ1-40 alone were not strong predictors of AD risk. In concordance with this review, a prospective case-cohort study with a mean follow-up of 8.6 years examined plasma Aβ1-40 and Aβ1-42 and the risk of dementia, including AD (van Oijen, Hofman, Soares, Koudstaal, & Breteler, 2006). High concentrations of plasma Aβ1-40, but not Aβ1-42, at baseline were associated with an increased risk of dementia. An increased plasma Aβ1-42/Aβ1-40 ratio was associated with reduced risk of dementia. In contrast to these findings, a later prospective population-based study of elderly men found that low plasma Aβ1-40 levels predicted incident AD (Sundelof et al., 2008). The latter finding, that plasma Aβ1-42 was not significantly associated with AD incidence, was consistent with that of the van Oijen study mentioned above.

Although there may be disagreement about the role of Aβ1-42 and Aβ1-40 in predicting AD risk, they may have a more clearly defined role in established disease. For example, Mehta et al. (2000) reported that mean plasma levels of Aβ1-40 were higher in their sample of patients with sporadic AD than in controls. Similarly, Mayeux et al. (2003) reported that levels of plasma Aβ1-40 and Aβ1-42 are elevated in the early stages of AD, but that they subsequently declined. The finding regarding the lower Aβ1-42/Aβ1-40 ratio also appears to be borne out in longitudinal research of disease

progression. A recently published study of AD patients reported a decrease in the plasma Aβ1-42/Aβ1-40 ratio over a period of 18 months (Rembach et al., 2013).

The current state of the literature suggests that plasma Aβ levels or ratios may have different risks for development of AD as opposed to their role in and with disease progression. Clearly, further investigations are required to confirm plasma Aβ levels or ratios as preclinical biomarkers for AD.

Hippocampal volume. The hippocampus plays a critical role in memory formation. Activation of hippocampal structures is crucial for new learning and declarative memory, especially episodic memory processes (Eichenbaum, 2003; Cipolotti et al., 2001). The brain pathology present in AD affects the hippocampus and other nearby regions at even early stages of the disease (Braak & Braak, 1991). These effects (for example, medial temporal lobe atrophy) can be seen on MRI.

Structural imaging has become increasingly useful in aiding the differential diagnosis of various kinds of dementia (Ramani, Jensen, & Helpern, 2006). Regions of brain tissue loss, as demonstrated by structural MRI, correlate with observed cognitive deficits (Frisoni et al., 2010; Vemuri et al., 2009). Furthermore, rates of total brain and hippocampal atrophy are sensitive markers of AD (McEvoy & Brewer, 2010). Additionally, a number of structural MRI studies have indicated that estimates of tissue damage or loss in characteristically vulnerable brain areas, namely the entorhinal cortex and hippocampus, are predictive of progression from MCI to AD.

Schuff et al. (2009) performed an MRI multicentre study that included 112 cognitively healthy older adults, 226 older adults with MCI, and 96 patients with AD. MCI and AD patients showed significant loss of hippocampal volume over 6 months, and accelerated loss over 1 year. Additionally, increased rates of hippocampal volume loss were associated with the presence of the ϵ4 allele in AD patients, and with lower CSF Aβ1-42 in MCI participants. The authors concluded that hippocampal volume change over time, as measured by structural MRI, has potential as a marker for AD.

The hippocampus was also one of the first brain regions to be identified as a target for stress hormones such as cortisol (McEwen, Weiss, & Schwartz, 1968). Subsequent studies have confirmed that the hippocampus is one of the regions primarily affected by the acute release of excess glucocorticoids and by chronic exposure to those hormones (Backman, Jones, Berger, Laukka, & Small, 2005b; McDonald, 2002). The hippocampus lies at the intersection of limbic, cognitive, and neuroendocrine regulatory circuits and may, therefore, be especially vulnerable to glucocorticoids/stress.

Alteration or damage to the hippocampus may set the stage for deleterious feedback that arises via neuroendocrine dysregulation. Ensuing hippocampal atrophy could cause further neuroendocrine dysfunction, possibly involving failure to down-regulate glucocorticoid receptors, where failure of the normal negative feedback to the HPA axis leads to the release of even more glucocorticoids. This release is, in turn, associated with further damage to the hippocampus, and so the destructive cycle continues (Maletic et al., 2007).

These cortisol elevations and consequent changes in hippocampal structure resulting from stress are linked with deficits in learning and memory function. Research conducted in rats indicates that a mild increase in glucocorticoid levels may enhance memory performance, but that large deficiencies or elevations disrupt memory performance (de Quervain et al., 2003; McEwen & Sapolsky, 1995; Roozendaal, 2000; Wolf et al., 2001). Similarly, in humans, Abercrombie, Kalin, Thurow, Rosenkranz, and Davidson (2003) reported enhanced memory performance following mild glucocorticoid elevations, but impaired performance following higher elevations. This result confirmed findings from an earlier study: Lupien et al. (1994) examined a group of 19 healthy elderly participants previously shown to differ in regard to their cortisol levels over a 4-year period. Those participants with increasing/high basal cortisol levels had significant impairments in hippocampal-dependent forms of memory compared to participants with decreasing/low basal cortisol levels. In a follow-up of the same cohort over a period of 5-6 years, Lupien et al. (1998) measured basal plasma cortisol levels annually over a 24-hour period in 51 healthy volunteer older adults. The authors found that total hippocampal volume and performance on hippocampal-dependent memory tasks in the increasing/high cortisol group was significantly reduced in comparison to that of the decreasing/moderate cortisol group. Taken together these findings provide support for the idea that exposure to progressively elevated glucocorticoid levels eventually compromises hippocampal integrity and therefore affects performance on hippocampal-dependent cognitive tasks (Squire, 1992).

Decades of research into the relationships between stress and cognition confirm that glucocorticoids play a vital role in the regulation of memory. A review performed by de Quervain and colleagues (de Quervain, Aerni, Schelling, & Roozendaal, 2009) concluded that there was evidence for the role of glucocorticoids in impairment of memory retrieval based on evidence from both animal and human studies.

The presence of APOE ϵ4 has also been associated with hippocampal atrophy. O'Dwyer et al. (2012) examined the volumes of deep grey matter structures in 22 healthy APOE-ϵ4 carriers and 22 non-carriers (20-38 years old). Their results indicated that, even in healthy young adults, the presence of ϵ4 was associated with hippocampal volume reduction. They suggested that the hippocampus might be particularly vulnerable to further degeneration in APOE-ϵ4 carriers as they enter middle- and old-age. In a sample of older adults (age range: 58-91 years), individuals with cognitive decline who were APOE-ϵ4 carriers had a faster rate of regional gray matter atrophy (affecting the hippocampi, temporal and parietal lobes, right caudate nucleus, and insulae) than non-carriers (Spampinato, Rumboldt, Hosker, & Mintzer, 2011).

Of contrasting note, however, is a recent study (Walsh, Slater, Nair, & Attia, 2013) that found no association between APOE-ϵ4 carrier status and hippocampal volume in a cohort of community-dwelling individuals with mild AD. These results imply that the presence of ϵ4 is, in itself, not sufficient to estimate pathological disease in early AD. This finding, then, confirms work by Henderson et al. (1995), who demonstrated that the APOE-ϵ4 allele is a risk factor for dementia but that homozygosity for the ϵ4 allele was not sufficient for the development of cognitive impairment and AD.

Psychosocial factors. Several psychosocial factors have been linked to risk for AD. The psychosocial factors of interest in this study include psychosocial stress and resilience, both of which are discussed below.

Psychosocial stress. The experience of stress, i.e., the encounter with a stressor, can alter brain circuitry to such an extent that it can have lasting effects on cognition (Arnsten, 2009; McEwen, 2007; Vasterling et al., 2012). In community-based studies, Neupert, Almeida, Mroczek, and Spiro III (2006) found an association between daily stressors and everyday memory failures, even after controlling for the effects of neuroticism, life-event stressors, and physical health. They also established that the number of life-event stressors correlated positively with the number of everyday memory failures (see also Stawski et al., 2006). Similarly, Caswell et al. (2003) found a negative association between chronic stress and information processing, episodic memory, and general cognitive function in older-adult caregivers of dementia patients.

Laboratory-based studies have shown that acute stressors also have negative effects on cognition in elderly persons. For instance, Lupien et al. (1997a) found that acute psychosocial stress manipulations, such as public-speaking tasks, reversibly

impaired memory performance in elderly adults (see also Luine, Villegas, Martinez, & McEwen, 1994). Wilson et al. (2003) reported that elderly people who were prone to experience psychological distress were also more likely to develop AD than were age-equivalent non-stressed individuals.

Johansson et al. (2010) published a 35-year longitudinal population study that investigated associations between midlife psychological stress and the risk of dementia. Participants in this sample (1462 females aged 36-60 years) were examined in 1968-69 and re-examined in 1974-75, 1980-81, 1992-93, and 2000-03. At the 35-year follow-up, 161 participants had developed dementia; 105 were diagnosed with probable AD. Frequent/constant stress, as reported in 1968 and 1974, was associated with this eventual development of AD. Reports of stress at one, two, or three examinations were related to a sequentially increased risk of developing dementia.

Although not explored in the current study but relevant to note in the context of stress and AD is post-traumatic stress disorder (PTSD), because severe psychological stress is associated with cognitive impairment and risk for AD. Furthermore, neuroimaging has demonstrated similarities between PTSD and AD on structural MRI (Tsolaki, Eleftheriou, & Karavida 2009). PTSD is stress-related psychopathology that can occur after an extreme emotional trauma that involved the threat of serious injury or death and resulted in intrusions, avoidance, negative alterations in cognitive functioning and mood, and changes in arousal and reactivity (American Psychiatric Association, 2013). PTSD has been linked to impaired cognition, predominantly in the domain of memory (Samuelson, 2011). A recent study investigated neuropsychological outcomes and PTSD in Iraq-deployed US Army soldiers (Vasterling et al., 2012). The study reported that PTSD was associated with enduring effects on cognitive functioning. Furthermore, research has shown a greater prevalence and increased risk of dementia (including AD) among US combat veterans (for more information, see Yaffe et al., 2010, and Qureshi et al., 2010).

At this point, it also seems pertinent to make brief mention of depression, a psychiatric condition known to be associated with psychosocial stress (Gilman et al., 2013; Stromberg, Backlund, & Lofvander, 2011; Siegrist, Lunau, Wahrendorf, & Dragano, 2012; Morris, Rao, & Garber, 2012) and cognitive impairment (Airaksinen, Larsson, Lundberg, & Forsell 2004; Papazacharias,& Nardini, 2012; Austin, Mitchell, & Goodwin, 2001; Steffens et al., 2006; Ganguli, Du, Dodge, Ratcliff, & Chang, 2006). Given these associations and therefore the possible confound of depression in

measurements of psychosocial stress and cognitive functioning, the presence of depressive symptoms was an exclusion criterion in this study and will therefore not be discussed further in this literature review. I shall discuss the specific details related to the exclusion of depression in the Methods section.

Resilience. There is no general consensus regarding a definition of resilience. However, some researchers regard it as an individual's ability to overcome adversity (Connor & Davidson, 2003; Schoon, 2006), and it is this conceptualisation that I will adopt here.

Given that resilience is a multidimensional characteristic, it is not surprising that it is affected by numerous factors, including age (Gooding, Hurst, Johnson, & Tarrier, 2012), sex (Samplin, Ikuta, Malhotra, Szeszko, & Derosse, 2013), education (Frankenberg, Sikoki, Sumantri, & Thomas, 2013), personality (Kim, Lee, & Lee, 2013), good psychological health (Petros, Opacka-Juffry, & Huber, 2013), adaptive social behaviour (Charney, 2004), social support (Wilks & Croom, 2008), and psychosocial stress (Taylor et al., 2010).

In a recently published longitudinal study, Terracciano et al. (2013) investigated whether personality traits are associated with resistance to clinical dementia, given that approximately 30% of cognitively normal older adults have, on autopsy, AD neuropathology.

The aforementioned studies indicate that there is a link between resilience and ageing, as well as a link between resilience and stress. Furthermore, both stress and resilience appear to play a role in the cognitive functioning of older adults, and in AD. These links, however, have been established relatively recently and further research is required, both for more nuanced exploration of these relationships and in different populations.

Sociodemographic factors. The sociodemographic factors of interest in this study are age, sex, and education. Each is discussed in turn below.

Age. Increased age confers the greatest risk for AD (Lindsay et al., 2002). AD is a disease predominantly of older adults, usually affecting people over the age of 65 years. Its prevalence doubles approximately every 5 years through to the 90s (Corrada, Brookmeyer, Paganini-Hill, Berlau, & Kawas, 2010; Jorm & Jolley, 1998).

Several factors may influence the rate at which individuals age. One such factor is stress. A sizeable body of literature suggests that stress plays a role in both biological ageing and age-related diseases. Empirical studies investigating indicators of biological

ageing have shown that one of the ways in which it is manifested is shortened telomeres. Telomeres are an area of repetitive nucleotide sequences that cap the ends of eukaryotic chromosomes (Capper, et al., 2007; Blackburn, 2000). These nucleotide sequences protect the ends of chromosomes from deterioration and help to prevent cell senescence. Telomeres are considered an index of cell age, where a shortened telomere indicates shortening of the cell's lifespan (Bekaert et al., 2007; Blackburn, 2000).

The experience of psychosocial stress has also been linked with ageing. Individuals who have had more lifetime experiences of psychosocial stress tend to display biomarkers of ageing such as higher oxidative stress, lower telomerase activity, and shorter telomere length. For example, Epel et al. (2004) demonstrated that women with the highest levels of perceived stress had shorter telomere lengths than those with the lowest such levels. Such findings have consequences for our understanding of how, on a cellular level, psychosocial stress may be linked with biological ageing. Factors, such as stress, shown to be associated with biological ageing may also then be associated with diseases arising from such biological ageing.

There are, however, age-related differences regarding exposure to, and reactions to, psychosocial stress. Birditt, Fingerman, and Almeida (2005) found that physically and cognitively healthy older people reported fewer interpersonal tensions, and experienced fewer stressful events, than did younger controls. Additionally, when they did encounter stressors, they were less reactive in their responses to them than were younger people. Similarly, Cohen & Janicki-Deverts (2012) found that, in adults, the experience of stress decreased with increasing age. In other words, older adults perceived their lives to be less stressful than younger adults did.

In direct contrast to the studies, reviewed above, reporting that, with increasing age, adults experience less stressful events and also perceive their lives to be less stressful, Krause (1999) reported that older adults are more likely than young adults to experience ongoing and chronic stressors, particularly relating to financial and medical concerns. The experience of these stressors, he argued, leads to negative side-effects, including detrimental impacts on cognition. Krause (2005) later proposed two explanations for why age-related variations in the stress response may occur. Firstly, he suggested that the developmental changes that arise during advanced old age may affect the nature and functioning of social networks. Secondly, he commented that older adults, particularly the old-old (75-84 years) and the oldest-old (85+ years), may be

more vulnerable to stress as a result of the physical and cognitive changes that can occur in later life.

While older adults may be more vulnerable to stress than younger adults, stressful experiences occur across the lifespan. Literature from both animal and human studies suggests that both lifetime and current experiences of stressors are associated with the acceleration of age-related cognitive decline. For instance, Bodnoff et al. (1995) found, using a spatial learning task, that middle-aged rats were more susceptible to the negative effects of chronic glucocorticoid exposure than were young adult rats. Similarly, in humans, Lupien et al. (1994) found that elderly participants with chronic glucocorticoid elevations showed significantly impaired explicit memory functioning relative to elderly participants with either decreasing cortisol over time or moderate current basal cortisol. McDonald (2002) suggested that good versus poor cognitive ageing might be the result of a combination of factors, one of which was exposure to chronic stressors and consequent elevated glucocorticoid levels. MacLullich et al. (2005) demonstrated that higher plasma cortisol levels in healthy older men were associated with more age-related cognitive decline (but not age-related brain atrophy).

In summary, although ageing is associated with increased risk for cognitive impairment and for the development of AD, chronological age is not a sufficient predictor of cognitive impairment either within or outside dementia. To elaborate, all individuals of the same age will not show the same degree of cognitive decline. Stress is one of the moderating factors in this relationship, as is the occurrence of age-related diseases such as AD.

Sex. Sex differences in the development of AD have been reported in studies from around the world. Dementia prevalence studies in Europe and North America, among others, report a higher risk of AD in women than in men (Brookmeyer, Gray, & Kawas, 1998; Di et al., 2002). A meta-analysis (Gao, Hendrie, Hall, & Hui, 1998) of 10 studies from 5 countries, covering the period 1966-1997, also reported that women are at higher risk of developing AD than men.

Age is thought to contribute to sex differences in the risk of developing AD. Andersen et al. (1999) found significant gender differences in incidence of AD after age 85 years, where women were at increased risk. Another theory for the observed sex difference in the risk of AD, supported by recent evidence, proposes that men have greater cognitive reserve than women (Schmidt et al., 2008). The concept of *cognitive reserve* (Manly, Jacobs, Touradji, Small, & Stern, 2002) arose from repeated

observations demonstrating that there did not seem to be a direct relationship between degree of brain pathology and clinical expression of such damage (Katzman, 1989). Cognitive reserve explains why individuals with age-related or AD pathology but with higher IQ (Pavlik, Doody, Massman, & Chan, 2006), years of education (Kemppainen et al., 2008), occupational attainment (Richards & Sacker, 2003), or participation in leisure activities (Fritsch, Smyth, Debanne, Petot, & Friedland, 2005) demonstrate less severe clinical or cognitive changes.

Sex differences in physiological and emotional responses to stress have also been reported (Chaplin, Hong, Bergquist, & Sinha, 2008; Wang et al., 2007). The direction of these differences suggest that women may experience a greater response to stress than men. Combined findings from three national surveys assessing psychological stress at three time points (1983, 2006, and 2009) showed that stress was higher in women than in men at all points (Cohen & Janicki-Deverts, 2012). Similarly, in a sample of 2816 people, (Matud, 2004) found that women scored significantly higher than men on measures of chronic stress and minor daily stressors, even after adjusting for sociodemographic variables.

Investigations of sex differences in functional brain responses to stress have also been performed. For instance, a functional MRI study of healthy young adults found that, in men, increased activity in the right prefrontal cortex was associated with the response to psychosocial stress. In women, however, increased activity in brain regions involved with emotion (including the limbic system) was associated with the stress response; additionally, these changes in blood-flow lasted longer in women than in men (Wang et al., 2007). Similarly, Kudielka and Kirschbaum's (2005) review concluded that adult men respond to laboratory-induced psychological stress with greater cortisol increases than women. The direction of this sex difference regarding the response to stress is in contrast to that discussed in the previous paragraph. Kudielka and Kirschbaum also proposed that sex differences in the structure of brain regions such as the limbic system, and in cognitive processing of a stressor, may be responsible for sexually dimorphic HPA-axis stress responses.

Education. Even in healthy older adults, there is a strong and well-established association between number of completed years of formal education (often termed 'level of education' in the literature) and cognitive test performance (Alley, Suthers, & Crimmins, 2007; Ganguli et al., 2010; van Hooren et al., 2007; Wilson et al., 2009). Furthermore, a lower level of education has been identified as a risk factor for AD

(Callahan et al., 1996; Evans et al., 1997; Qiu, Backman, Winblad, Aguero-Torres, & Fratiglioni, 2001; Stern et al., 1994b). In a sample of 373 AD patients and 559 healthy control participants, Sando et al. (2008a) found that education had a consistently protective effect on the risk of developing AD in a dose-dependent manner in both men and women, even after adjusting for the number of APOE-ϵ4 alleles. They reported that the odds ratio for developing AD was reduced significantly in individuals with 8-9 years of education compared to those with 6-7 years, and was further reduced for those with 10-18 years of education.

The protective role of higher levels of education is understood in the context of cognitive reserve because education is considered a proxy measure of cognitive reserve (Meng & D'Arcy, 2012). As noted earlier, there is wide individual variation in the likelihood of dementia with several possible contributory factors; cognitive reserve, with its link to education, adds to this variation. Part of the cognitive reserve hypothesis postulates that education plays a role in delaying the manifestation of dementia symptoms by enabling compensatory techniques that allow individuals to cope more effectively with pathological brain changes (Stern, 2009).

The cognitive reserve hypothesis is further supported by Roe and colleagues (Roe, Xiong, Miller, & Morris, 2007), who found that older adults (age 65+ years) with more education were less likely to have a diagnosis of dementia. Their higher levels of education may have enabled them to cope with AD brain pathology for a longer period of time therefore delaying the manifestation of clinical symptoms. They concluded that education is predictive of dementia status in individuals with neuropathologic AD.

Studies have investigated links between education and psychosocial stress. Research carried out in 1031 adults demonstrated that better-educated adults had fewer physical symptoms and less psychological distress (Grzywacz, Almeida, Neupert, & Ettner, 2004). Although the better-educated individuals in the sample reported more daily stressors, those stressors were less severe than those reported by those with less education. Furthermore, the authors reported that the subjective experience of stressors seemed to promote more negative changes in daily health in those who had not completed high school compared to those who had completed high school or who had at least some college education. Similarly, in adults aged 18 years and older (mean age 44.6 years), Cohen and Janicki-Deverts (2012) found that stress increased with decreasing levels of education.

Alzheimer's Disease Research in Africa

To my knowledge, there has been no African research examining the combination of questions investigated in this dissertation. Indeed, studies relating to AD in general in African populations are scarce (see Figure 2), and those that have been conducted have been predominantly of a (limited) epidemiological nature.

An African study has reported an AD prevalence rate of 1.41% in Ibadan, Nigeria (Hendrie et al., 1995). Overall dementia prevalence rates have been reported as 10.1% in South-West Nigeria (Gureje et al., 2006); 6.4% in Jos, Nigeria (Ochayi & Thacher, 2006); 2.79% in Zaria, Nigeria (Yusuf, Baiyewu, Sheikh, & Shehu, 2011), 4.5% in Assuit, Egypt (Farrag, Farwiz, Khedr, Mahfouz, & Omran, 1998); 2.2% in Ibadan, Nigeria (Hendrie et al., 1995); 2.6% in rural Benin, West Africa (Guerchet et al., 2009); 8.1% in the Bangui, Central African Republic and 6.7% in Brazzaville, Congo (Guerchet et al., 2010). The latter two studies suggest that the prevalence of dementia in urban areas of central Africa is similar to that observed in HICs.

Many of the studies cited above were conducted in Nigeria. Some of this work was performed in Ibadan, where one particular study, the Indianapolis-Ibadan Dementia Study that I discussed previously as regards APOE-ϵ4, compared the prevalence of AD in two community-dwelling samples. As mentioned, one of the samples was drawn from Ibadan, Nigeria, and the other from an African-American population in Indianapolis, United States. This study reported that in adults over 65 years old in the Ibadan sample, age-adjusted prevalence rates of dementia and AD were 2.29% and 1.41% respectively (Hendrie et al., 1995). These rates were markedly lower than those for the Indianapolis sample where prevalence rates for dementia and AD in a combined sample of individuals from nursing homes and in the community was 8.24% and 6.24% respectively.

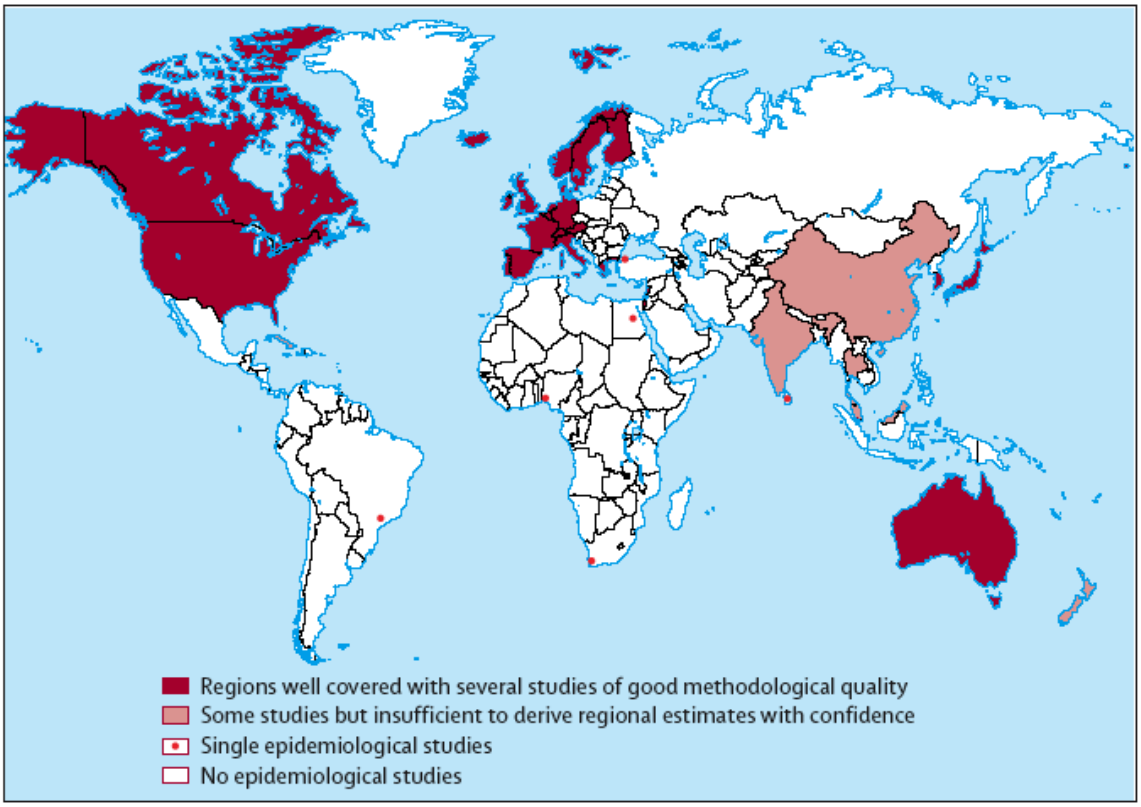


Figure 2. Global research evidence on the prevalence of dementia (Ferri et al., 2005). Those regions coloured in red (North America, Europe, Japan, and Australia) boast several studies of good methodological quality. The pink regions consist of some epidemiological studies but they are insufficient in quality or quantity to provide estimates that are representative of the regional dementia prevalence. The white regions lack completely, or almost completely, epidemiological studies, and those with a red dot represent region sites of single studies.

Given the relatively limited scope of the studies described above, the prevalence of AD in Africa remains largely unknown. It is only recently that systematic hospital surveys or community-based studies of AD have been initiated in Africa. In 2005, Alzheimer's Disease International reviewed epidemiological data on dementia to reach a consensus estimate of prevalence in each world region. Their findings supported the trend for a somewhat lower prevalence of dementia in LAMICs as opposed to that in HICs (Ferri et al., 2005).

Estimations of the prevalence rates for dementia in sub-Saharan Africa have been approximately 2.4% (Ferri et al., 2005). This low rate derives from one good-quality study, discussed previously, which was conducted in Ibadan, Nigeria (Hendrie et al., 1995).

A recent systematic review was performed to estimate the prevalence of dementia in Africa in persons over the age of 50 years (George-Carey et al., 2012). This review, modelled on 10 studies, included community-based studies conducted in LAMICs in Africa that reported dementia prevalence. Based on this collection of studies, the authors reported an overall dementia prevalence of 2.4% and that dementia prevalence was highest among females aged 80 years and over. AD was the most prevalent cause of dementia, and the main risk factors were increasing age, female sex, and cardiovascular disease. These risk factors correspond with those reported in previous studies African studies; the latter showed the major risk factors for AD to be age, female gender, BMI less than 18.5, illiteracy, and vascular disease (Farrag et al., 1998; Kalaria et al., 2008; Ochayi & Thacher, 2006; Yusuf et al., 2011).

In South Africa, a study on prevalence rates of dementia in the urban black population is currently being conducted at the University of the Free State in Bloemfontein (University of the Free State, 2010). The pilot study involved a test group of older adults (age ≥ 65 years) from 250 households in the township of Mangaung. In this sample, 6% were identified with possible age-related dementia. The latter are to be followed up with more extensive confirmatory diagnostic assessment. This finding of a prevalence rate over 5%, albeit in a small sample drawn from a restricted geographic region, goes some way in dispelling the myth that AD is linked to European ethnicity and that it is not prevalent in black communities (Steyn, 2010). These data also suggest that prevalence rates of dementia in urban Black African communities in South Africa are higher than initially estimated.

Possible reasons for earlier studies providing relatively low estimated rates of dementia prevalence in African populations include a low life expectancy at birth and differential survival rates. Currently, the average life expectancy at birth in sub-Saharan Africa is 53 years; this is largely a result of the high rates of HIV infection (Lawn, Harries, Anglaret, Myer, & Wood, 2008). The low life expectancy in sub-Saharan Africa will therefore reduce the total number of cases of AD, which, as noted earlier, is a disease predominantly of older adults and which generally presents 65 years of age. However, for those individuals who do not contract HIV in their youth, life expectancy is likely to increase. For example, Statistics South Africa (Statistics South Africa, 2013) estimated that the Western Cape province of South Africa has the highest life expectancy for males and females. Males were estimated to have a life expectancy of 64.2 years and females approximately 70 years. Thus, an age-associated increase in

prevalence of AD is still likely to be seen, particularly in places such as the Western Cape.

Despite a relatively low life expectancy in sub-Saharan Africa, projections from the United Nations indicated that the number of adults aged 60 years and over will increase exponentially from 5% to 8% of the population by the year 2050 (United Nations Population Division, 2006). In South Africa, the population of older adults is expected to increase from 3.3 million to 6.4 million. This equates to an increase from 7% to 13% of South Africa's population (Kalula et al., 2010). Thus, the prevalence of dementia and AD in this country is expected to increase exponentially over the next several decades.

Currently, there are no studies examining whether prevalence rates for AD are similar in South Africa and Western populations. If there is a real trend for lower prevalence rates of AD in African populations, then there may exist unique, culture-based, dietary, or environmental factors, or possibly protective factors, for cognitive impairment in African populations. This doctoral dissertation is not a prevalence study, however; its main aim is to identify factors associated with cognitive functioning in older adults across a continuum from healthy to impaired cognition. The identification of such factors in different African populations is necessary, at least as an initial step, in order to identify possible explanations for Africa's (lower?) prevalence rates of AD.

Cross-Cultural Issues in Neuropsychological Testing

As mentioned in the *General Introduction*, neuropsychological testing contributes pivotally to the diagnostic assessment of older adults. However, performance on cognitive tests represents, to a certain extent, culturally learned abilities. Variations in cultural and environmental settings (e.g., differences in the types of learning materials that are available; whether students have the opportunity to work independently as well as in groups) may give rise to the development of different patterns of cognitive abilities (Ardila, 1995). Although performance on verbal tests is obviously influenced heavily by cultural variation, the impact of culture is also present for performance on visuospatial and non-verbal tests; clinical neuropsychologists no longer consider these kinds of tests as being, by default, culture-fair (Rosselli & Ardila, 2003). Many definitions exist for the word "culture" but broadly defined, it refers to the set of characteristics of a particular group of people that incorporates their language,

religion, social habits, and ways of thinking and behaving within a social group (Hofstede & Hofstede 2005). It is developed though interaction among individuals in a community and it has a large influence on human nature (Parrish & Linder-vanBerschot 2010).

Some cross-cultural factors that may influence neuropsychological performance include the effects of culture itself (Manly et al., 1998), home language (MacIntyre & Gardner, 1994), socioeconomic status (SES) (Rabbitt, Donlan, Watson, McInnes, & Bent, 1995), and level and quality of education (Lezak, Howieson, & Loring, 2004; Manly et al., 2002; Ostrosky-Solis, Ramirez, & Ardila, 2004; Shuttleworth-Edwards et al., 2004).

Most neuropsychological instruments have been developed and validated in HICs, and most are therefore normed on populations that, generally, have higher levels and quality of education than do those in LAMICs. Thus, the reliability, validity, specificity, and sensitivity of existing cognitive measures can be compromised when administered to individuals from LAMICs. Differences in cognitive performance among different cultural groups may increase the possibility of overdiagnosing cognitive impairment (Potter et al., 2009). Hence, there is general agreement among clinicians that most neuropsychological measures do not have adequate diagnostic accuracy when administered to individuals who are not middle- to upper-class, of European descent, well-educated, first-language English speakers (Boone, Victor, Wen, Razani, & Ponton, 2007; Manly, 2005).

To place this problem in the South African context, under apartheid rule, the type and quality of education was determined by a system of "racial" classification resulting in varying quality of education across different ethnic groups. For instance, Shuttleworth-Edwards and colleagues (2004) showed that black South Africans, especially those with a low quality of education, performed more poorly on neuropsychological tests than white South Africans. However, such effects on cognitive performance have been accounted for more by socio-cultural factors that typify a particular ethnic group, than the ethnic traits themselves (Shuttleworth-Edwards et al., 2004). These results showed that quality of education was a stronger predictor of cognitive performance than race or ethnicity. This does not mean, however, that factors relating to ethnicity should not be considered in the context of cognitive performance. Indeed, assessing cognitive performance across different ethnic groups without suitable methods of standardization is cause for concern, especially in the context of a

diagnostic process (Manly et al., 1998; Okazaki & Sue, 2000; Stricks, Pittman, Jacobs, Sano, & Stern, 1998). Individuals from particular ethnic groups who were afforded a higher quality of education are more likely to have been exposed to formal cognitive testing procedures. Nell (2000) emphasized the role of 'test wiseness': the concept that individuals with higher quality and level of education perform better in test-taking environments at least in part because of greater familiarity with the actual test-taking process.

Data such as these reaffirm the notion that "race", being a socially constructed concept, is not in itself responsible for performance on neuropsychological measures. Rather, it is the factors that are linked with race that are more likely to be responsible; these factors include quality of education, language, and SES (Shuttleworth-Edwards et al., 2004; Shuttleworth-Jordan, 1996; Ardila, 1995).

Regarding the influence of language on cognitive test performance, it stands to reason that individuals who are assessed in a language that is not their primary language may be disadvantaged; their scores may not reflect their true cognitive abilities accurately. For example, Boone et al. (2007) examined the relationship between neuropsychological scores and ethnicity, language, and acculturation variables in a large patient population. The authors found that cognitive scores on several measures were significantly higher in patients for whom English was a first language compared to patients for whom English was a second language.

Regarding the influence of SES on cognitive test performance, it appears that lower SES is associated with poorer performance (Kyle, Fox, & Whalley 2010; Sarsour et al., 2011; Brooks-Gunn, & Duncan 1997; Currie, 2005; Malecki, & Demaray 2006). This association was confirmed in a recent study of older adults with cirrhosis from centers in three cities, namely, Virginia, Ohio, and Rome (Bajaj et al., 2013). Analyses revealed a strong positive association between SES (estimated from employment level and personal income) and cognitive performance, irrespective of age, education, and location.

As discussed in the paragraphs above, there are several cross-cultural issues which arise in neuropsychological assessment. It is evident that addressing cultural diversity in cognitive assessment and performance is a critical part of neuropsychological research and practice (Manly, 2008). This cultural diversity should be taken into consideration especially when diagnoses are informed by such assessments. Compared with resources available in HICs, poor access to resources in

populations from LAMICs increases the likelihood of fewer years and a lower quality of education. The latter increases the probability of a poorer performance on cognitive tests which may lead to an incorrect diagnosis being made, if the diagnosis relies heavily on cognitive performance. Thus, it is perhaps more difficult to diagnose cognitive impairment and AD accurately in LAMICs because of problems surrounding the psychometric properties of the tests that are currently used. This means that adequate consideration should be given to non-organic factors, such as those listed above, that might affect assessment and diagnostic decisions.

Consideration of cross-cultural factors is relevant in the context of the current study because the group of South African older adults assessed here comprises individuals from heterogeneous cultural, educational, and SES backgrounds. Furthermore, the neuropsychological measures used in this study were developed in Europe and North America, and were standardised on samples from HICs. To accommodate for this some of the test items needed to be altered in order to be appropriate for this South African sample. I shall discuss these changes in more details in the *Methods* section. Additionally, the cognitive performance of the AD participants in this study was not compared to norms from HICs; rather, cognitive performance was compared to the control participants in this sample. This had the benefit of reducing errors that might otherwise have been present if the cognitive performance in my sample had been compared to norms for HICs.

Summary

A multi-factorial aetiology suggests there is no specifically defined pattern of factors associated with the development of cognitive impairment in older adults. Furthermore, such factors may vary in different environments, in different family settings, or with different genetic dispositions. The literature review above has discussed several factors associated with age-related cognitive impairment and AD, including a range of physiological, genetic, psychosocial, and sociodemographic factors. This is not an exhaustive list of factors related to the development of cognitive impairment, however, but it is a list of factors known to be associated with both stress and cognitive impairment in AD.

All of these factors have been investigated previously within HIC populations. Some have been explored in terms of their relationships with each other; for example,

psychosocial stress and APOE-ϵ4, cortisol and hippocampal atrophy, stress and Aβ. To my knowledge, however, there is no study that explores the inter-relationships of all of these factors, together, in one sample.

Furthermore, there are few LAMIC studies investigating these variables in older adults, both cognitively healthy and demented. Certainly, no research of this kind has been performed in a South African population. Thus, my research focuses on psychosocial stress, cortisol, the APOE-ϵ4 allele, Aβ, and hippocampal volume in a sample population of older South African adults from the Western Cape region with and without cognitive impairment. I aimed to examine the independent relationships of these factors with cognitive functioning in healthy older adults and in patients with early-to-moderate AD (i.e., to examine whether the relationships changed across a spectrum of cognitive functioning in these two groups), and to examine the associations of these factors with one another.

Study Aims and Hypotheses

The general aim of this study was to explore, in a South African population sample, the relationships between psychosocial stress, cortisol, APOE-ϵ4, Aβ, hippocampal volume, and cognitive functioning in cognitively healthy older controls and in participants with Alzheimer's disease. I aimed to investigate not only the relationships between these psychosocial, physiological, and genetic variables and cognitive impairment, but also the relationships of those variables amongst each other. Figure 3 depicts, in sketch form, the study's aims; it is a schematic representation of the separate (boxed) research areas of interest here. This diagram speaks to the central theme of this thesis: that there are numerous factors associated with the development of cognitive impairment, and that one such factor is stress, as both a psychosocial and physiological construct. Furthermore, some of these factors are inherent, and some are modifiable in early life but less so later in life. The figure also shows that stress (psychosocial and physiological) is proposed to have lasting effects on cognitive function and brain structure, probably via its instigation of biochemical changes in the brain. These possible effects are measurable by neuropsychological testing, neuroradiological imaging, and biochemical tests of blood samples.

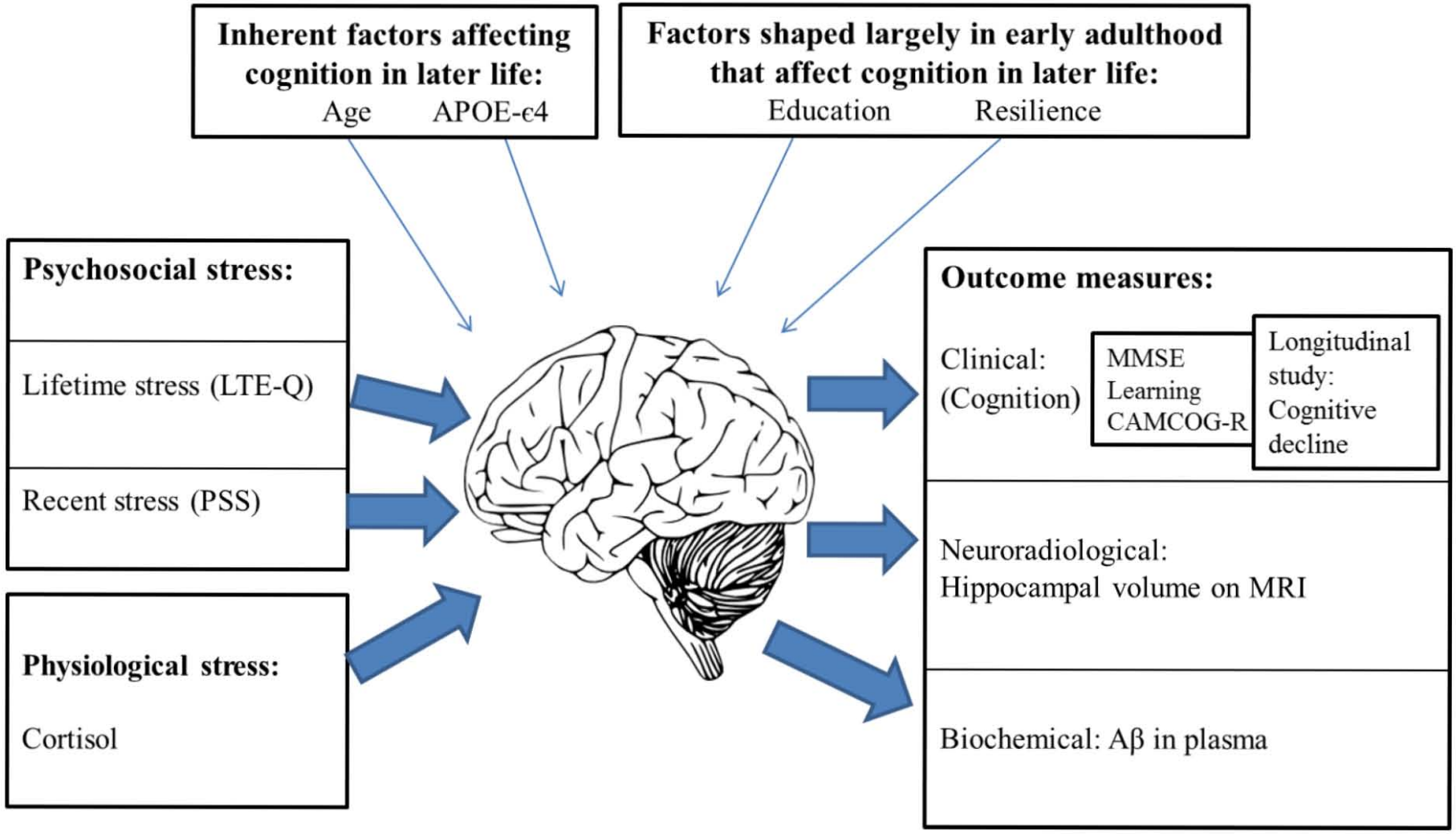


Figure 3. Schematic representation of research areas of interest. APOE-ϵ4 = apolipoprotein- ϵ4; Aβ = beta-amyloid; CAMCOG-R = Cambridge Cognitive Examination-Revised; LTE-Q = List of Threatening Life Events Questionnaire; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; PSS = Perceived Stress Scale.

In addition to the aims outlined above, I also sought to explore the role of demographic factors, such as age and education, and levels of resilience, in determining their relationship to cognitive functioning in this sample of South African older adults. The variables listed earlier (psychosocial stress, cortisol, APOE- ϵ4) are associated with cognitive functioning, and with the sociodemographic variables listed above, and are thus explored in one large model.

Because this is not an experimental study, and because the predictor variables do not influence cognition in isolation from each other, I used a hierarchical regression model to explore all of their relationships together. However, I also wished to establish the initial direction of bivariate associations as well as between-group differences, and so tested the hypotheses listed below.

The first set of hypotheses related to the putative risk factors of psychosocial stress, physiological stress (cortisol), and cognition in cognitively healthy older adults and in participants with AD. *Hypothesis 1a* stated that AD patients would have higher levels of current psychosocial stress, more lifetime experiences of traumatic life events (recent and remote stress), and higher baseline cortisol levels than controls. *Hypothesis 1b* stated there would be a larger positive association between psychosocial stress and cortisol levels among AD patients than among controls. *Hypothesis 1c* stated that levels of psychosocial stress and cortisol would be negatively correlated with cognitive performance within each group separately and across the entire sample.

The second set of hypotheses related to resilience, psychosocial stress, and education, and how they are associated with each other in controls and AD patients. *Hypothesis 2a* stated there would be an inverse association between resilience and psychosocial stress in both groups. *Hypothesis 2b* stated there would be a positive association between education and resilience in both groups.

The third set of hypotheses related to APOE-ϵ4 and its association with both psychosocial and physiological stress. *Hypothesis 3a* stated AD patients would have a higher allelic frequency of APOE-ϵ4 than controls, and *Hypothesis 3b* stated those AD patients carrying the ϵ4 allele would perform more poorly on a measure of overall cognitive function than those who did not carry it. Finally in this set of hypotheses, *Hypothesis 3c* stated AD patients with higher baseline cortisol levels and presence of the ϵ4 allele would perform more poorly on a measure of overall cognitive function than would AD patients with lower baseline levels of cortisol and an absence of APOE-ϵ4.

The fourth set of hypotheses related to plasma Aβ and its association with psychosocial and physiological stress. *Hypothesis 4a* stated AD patients would have a lower ratio of Aβ1-42/Aβ1-40 than controls, and *Hypothesis 4b* stated AD patients with high levels of psychosocial stress and cortisol would have a lower plasma Aβ1-42/Aβ1-40 ratio than AD patients with low levels of psychosocial stress and cortisol.

The fifth set of hypotheses related to the neuroimaging component of this study. They aimed to investigate hippocampal volumes in both groups and their association with psychosocial stress, as measured by the PSS, and physiological stress, as measured by baseline levels of circulating cortisol. *Hypothesis 5a* stated AD patients would have smaller hippocampal volumes than controls, and *Hypothesis 5b* stated that AD patients with higher baseline cortisol levels and the APOE-ϵ4 allele would have smaller adjusted total hippocampal volume than patients with low baseline cortisol levels and no APOE-ϵ4.

As mentioned previously, after exploring these initial relationships I then used each of these factors (age, education, APOE-ϵ4, psychosocial stress, and cortisol) as predictor variables in a large regression model that aimed to determine their independent and interactive effects on cognition. This modelling step was an exploratory analysis as I did not have a specific hypothesis regarding which factors, other than age, would be significant and/or unique predictors of cognitive functioning.

Methods

Participants

Alzheimer's disease patients (n_{AD} = 65) were recruited from a variety of sources: a nursing home located near Cape Town, Groote Schuur Hospital's Memory Clinic and geriatric outpatient clinics, and general practitioner (GP) referrals. Most of these patients had been diagnosed, prior to entering the study, as having mild to moderate AD, or possible or probable AD, in terms of NINCDS/ADRDA criteria (McKhann et al., 1984). Some were referred directly to the study by the Groote Schuur Hospital (GSH) Memory Clinic. Those participants who had not yet been diagnosed were assessed by a senior neurologist and were identified as cognitively healthy controls, or as mild to moderate stage possible or probable AD based on a detailed medical history, physical exam, bedside cognitive tests, and a brain CT scan in some cases. We selected patients who were in the mild to moderate stages of possible or probable AD so that they would be able to consent to procedures and to complete the questionnaires and cognitive tests. Patients in the severe stage of the disease were therefore excluded from participation.

Control participants (n_{HC} = 69) were healthy, community-dwelling, independent volunteers. They were recruited from communities in and around Cape Town via word-of-mouth advertising. I obtained general health information from all participants using a clinical interview.

All participants were over the age of 60 years. Other inclusion criteria included literacy and a good command of either English or Afrikaans, which was established based on comprehension and answering of questions during the screening procedure. Participants who scored above the cut-off score for depression were excluded. Figure 4 illustrates the participant enrolment process.

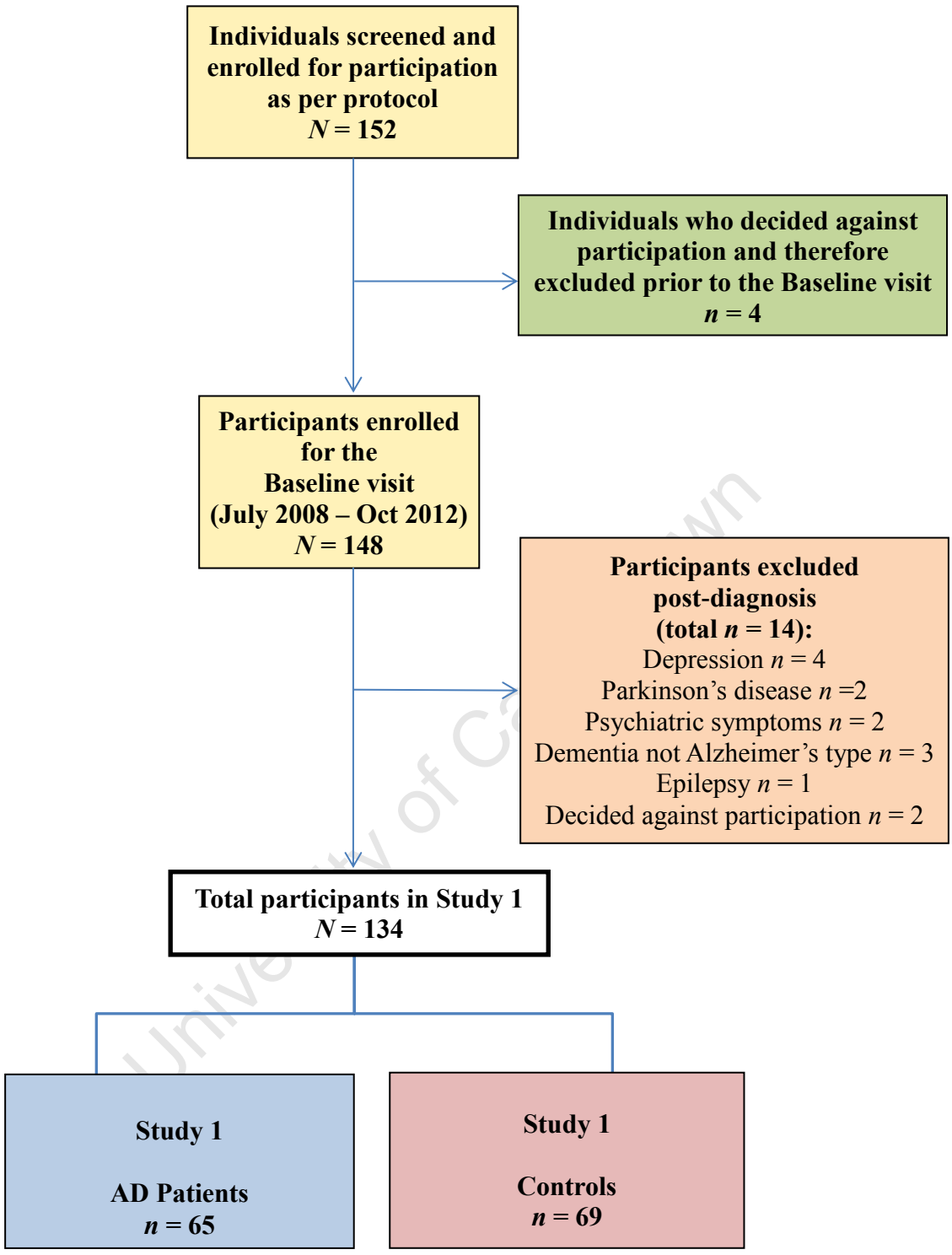


Figure 4. Diagram illustrating the number of participants (healthy controls and AD patients) enrolled in Study 1 (the cross-sectional study), as well as details relating to exclusion.

Table 1 provides a detailed breakdown of the inclusion and exclusion criteria for participation in this study.

Only a subset of these participants (N = 40) was selected for the Aβ analyses. Participants' plasma samples for the Aβ analyses were selected based on their age (to ensure the groups were age-matched) and how recently their samples had been obtained (Controls n = 10, AD patients n = 30). More AD patients than controls were selected for this subset of participants because I was primarily interested in investigating levels of Aβ in patients with AD, as this is where most of the variation might occur.

Similarly, only a subset of participants (N = 40) was selected for the MRI component of this study. For the MRI scans, participants who were willing to have an MRI scan were selected according to age, as I wanted to match the groups as closely as possible in this regard. Five of the selected participants (4 patients and 1 control) did not complete the scan, and so the final sample size for this component of the study was N = 35 (Controls n = 14, AD patients n = 21).

The reason for performing the Aβ and MRI assessments in only a subset of participants was due to resource constraints; study funding only allowed for 40 MRI scans and one 96-well assay, including standards and controls, for the Aβ (i.e., 40 participants' samples in duplicate).

Table 1
Inclusion and Exclusion Criteria for Participation in the Study 1

Inclusion criteria	**Exclusion criteria**
Age ≥ 60 years Literacy Basic ability to speak, read, and write Language Fluent in English Cognition (controls) Normal for age range Cognition (patients) Mild to moderate or possible/probable AD Informant Availability of close relative or similar who could provide information about changes in cognitive function	Medical health history Diagnosis of: • HIV/AIDS • Uncontrolled hypertension • Uncontrolled diabetes mellitus • Any other medical condition that, in the opinion of the investigator should preclude the patient from participation • Oral steroid treatment Psychiatric history • Presence of any major disorder (e.g. depression; Geriatric Depression Scale score > 7) Neurological history • Presence of any major disorder (e.g., Parkinson's disease, Huntington's disease) • Recent (past 6 months) stroke Substance use • Any history of alcohol or drug abuse Heavy smoking (> 20 cigarettes per day) Mini-Mental State Examination < 12 No access to a freezer at home (for storage of saliva samples)

Research Design and Setting

Most study procedures were conducted in the Division of Neurology at Groote Schuur Hospital, at a nursing home, or at the participant's residence. Irrespective of the venue, all participants were tested in an isolated, quiet room at similar times of day, between the hours of 09h00 and 11h30. MRI scans were performed at the Cape Universities Brain Imaging Centre (CUBIC) on the University of Stellenbosch Health Sciences Campus.

Materials

This study formed part of a larger research programme that employed numerous instruments to measure physiological and biochemical markers of stress, genetic risk factors, brain volume, lifetime exposure to traumatic events, current stress levels, and cognitive, behavioural, affective, interpersonal, and adaptive functioning measures. Only a subset of those instruments was used in the current study, and only those are described here. The instruments selected for this study were chosen because they relate directly to its aims and hypotheses. Some of these instruments had been used with some success in previous studies in South Africa (e.g., Heckmann et al., 2004; Lenger, de Villiers, & Louw, 1996). Only the non-copyrighted materials used in this study have been reproduced as appendices.

Sociodemographic questionnaire. Participants completed a questionnaire, created specially for this study, which asked for information on their age, sex, race, home language, education, and health (see Appendix A). Where necessary, the participant's caregiver/spouse/guardian/family member (hereafter referred to as the informant) was asked to corroborate this information.

Psychosocial stress measures. I used the *List of Threatening Life Events Questionnaire* (*LTE-Q*; Brugha & Cragg, 1990) to identify lifetime stress and whether participants had ever experienced certain traumatic life events, such as losing a loved one or being fired from a job. This instrument consists of 11 statements. It required participants to indicate whether or not they had experienced any of the events described by those statements, and, if so, whether the event occurred within the past 6 months (recent stress) or earlier in their life (remote stress). Participants were then required to rate the impact a particular event had on their life at the time of its occurrence (*none* = 1, *some* = 2, *significant* = 3). If a participant had not experienced any of these events,

then s/he would have obtained a minimum score of 0. If a participant had experienced every event both in the last 6 months and more than 6 months ago and had rated each event as having a significant effect on his/her life, then his/her total score on this measure would have been the maximum, 66 points. Hence, higher scores on this instrument indicate more experiences of traumatic life events that have had some or a significant impact on one's life.

The questions asked in this measure refer to significant life events that I expected would remain well-remembered by patients in the mild to moderate stages of AD. The developers of this instrument have shown that the LTE-Q has high test-retest reliability and good agreement with informant information relating to life events (Brugha & Cragg, 1990). To my knowledge, this instrument has not been used in a previously published South African research study.

I administered the *Perceived Stress Scale (PSS;* Cohen, Kamark, & Mermelstein, 1983). This 14-item scale assesses the degree to which situations in one's life over the past month are appraised as stressful. The items are designed to detect how unpredictable, uncontrollable, and encumbered participants find their lives. To score this instrument, scores on the seven positive items are reversed (e.g., *0 = 4, 1 = 3, 2 = 2,* and *4 = 0*), and then scores for all 14 items are summed; the minimum score is 0 and the maximum score is 56 points. Higher scores indicate that the individual perceives him or herself as having experienced a stressful life over the last month.

The developers have reported that the PSS shows adequate reliability and validity (Cohen, Kamarck, & Mermelstein, 1983). This instrument has been used previously in South African research investigating depressive symptoms and perceived stress in adults (Hamad, Fernald, Karlan, & Zinman 2008).

In this study, the PSS was used as the primary indicator of 'psychosocial stress'. In contrast to major life events (such as those measured by the LTE-Q) which are relatively rare, daily stressors occur frequently and analysis of such can provide a more accurate picture of how stressful one's life currently is (Stawski, Sliwinski, Almeida, & Smyth, 2008). Furthermore, the PSS is the most widely used measure of stress appraisal, it correlates well with life-event scores, and it has been found to be a stronger predictor of several health outcomes relative to life-event measures (Cohen et al., 1983; Cohen, Kessler, & Gordon, 1995).

Affective, behavioural, and adaptive functioning questionnaires. I used the *Deterioration Cognitive Observee* (*DECO*; Ritchie & Fuhrer, 1996) to provide

collateral information regarding the participant's level of cognitive and functioning abilities. The DECO is a 19-item Likert-type scale that measures aspects of behaviour and cognition (activity level, semantic and visual memory, memory for places, events, and procedures, visuospatial performance, and new skill learning). In accordance with standard procedure, it was completed by an individual, nominated by the participant, who had had at least monthly contact with the participant over a period of 3 years.

This questionnaire required the informant to rate the participant's level of functioning, relating to a number of everyday situations, compared to 1 year previously. The informant needed to indicate for each statement whether the participant's functioning or ability to perform a particular task was either *better or about the same* (a score of 2), *not as well* (a score of 1), or *much worse* (a score of 0). Hence, the minimum score is 0 (decline in functioning across all areas) and the maximum score is 38 (intact functioning). Scores lower than 30 have been established by Receiver Operating Characteristics analysis as indicating a high probability of dementia within a general population sample (Ritchie & Fuhrer, 1996).

Psychometric studies of the DECO have shown that it has good face validity as well as high test-retest and inter-rater reliability, and that it does not show bias with regards to education or social class (Ritchie & Führer, 1996). The Xhosa translation of the DECO has been used previously in South African research studies of early-onset AD and it has been recommended as a possible screening measure for dementia in older adults in South Africa (Heckmann et al., 2004; Lenger et al., 1996).

The *Bristol Activities of Daily Living Scale* (*BADLS*; Bucks, Ashworth, Wilcock, & Siegfried, 1996) provided a short assessment of the functional ability of participants, focusing on tasks such as handling finances, dressing, and eating. The same informant who completed the DECO completed this 20-item scale. The informant rated the participant's ability to perform tasks on a scale of: 0 = *able to perform task independently/unobservable*; 1 = *able to perform task with some instructions/prompts*; 2 = *able to perform task with assistance*; 3 = *unable to perform task independently and requires full assistance.* The minimum score for this measure is 0 (totally independent) and the maximum score is 60 (totally dependent).

The BADLS has good test-retest reliability and validity (Lezak et al., 2004). In terms of relevant cross-cultural use, it was administered to an elderly South African sample in a study investigating the reliability and validity of a Xhosa version of a health-related quality of life measure (Jelsma, Mkoka, Amosun, & Nieuwveldt. 2004).

I used the *Connor-Davidson Resilience Scale (CD-RISC;* Connor & Davidson, 2003) to obtain a self-rated assessment of resilience. Each of the 25 items on this instrument is rated on a 5-point scale (0 = *not true at all*; 1 = *rarely true*; 2 = *sometimes true*; 3 = *often true*; 4 = *true nearly all the time*), where higher ratings indicate greater resilience (total score out of 100). This instrument required participants to think about how they felt over the last month when answering each statement. The developers note that the scale has been tested in both the general population and in clinical samples, where it has displayed good psychometric properties, including good internal consistency, test-retest reliability, and convergent validity with other measures of stress and endurance. This instrument has been used previously in South African research focusing on perceived social support in youth (Bruwer, Emsley, Kidd, Lochner, & Seedat, 2008).

I administered the *Geriatric Depression Scale (GDS;* Yesavage et al., 1982) as a screening measure to detect the presence of symptoms of depression. Hence, individuals who scored above 7/15 (i.e., who self-reported the presence of at least moderate depression) were excluded from participation. The GDS, in its original form, is a self-report 30-item scale that was developed as a basic screening measure for depression in older adults. Higher scores indicate a greater number of symptoms of depression. For this study, participants were required to answer a 15-item version of the scale. Both the original and shortened versions of the GDS display high internal consistency, test-retest reliability, and validity (Yesavage et al., 1982). The 15-item version has been established as an instrument suitable for diagnosing depression in elderly populations (de Craen, Heeren, & Gussekloo, 2003). This measure has been used previously in a South African study examining depression and social support in elderly people (Rodriguez, Brathwaite, & Dorsey, 2002).

Neuropsychological test battery. The *Cambridge Cognitive Examination for Mental Disorders of the Elderly-Revised* (CAMCOG-R; Huppert, Brayne, Gill, Paykel, & Beardsall, 1995) provided a baseline measure of general cognitive functioning. This instrument is the revised version of a cognitive examination section that forms part of the Cambridge Mental Disorders of the Elderly Examination-Revised. The CAMCOG-R was originally devised as a screening tool for dementia in older adults (Leeds, Meara, Woods, & Hobson, 2001). It consists of 67 items divided into eight cognitive domains: Orientation, Language, Memory, Attention, Praxis, Calculation, Abstract Thinking, and Perception. The CAMCOG-R has a maximum attainable score of 105, and it requires

approximately 25 minutes for administration. It has high test-retest and inter-rater reliability, and it is sensitive in the detection of dementia and to changes in cognition over time (Hobson & Meara, 1999; Leeds et al., 2001).

Some of the CAMCOG-R items were altered, however, because they were not suitable for use with South African participants. The altered items included those related to geographical places and to historical figures and events; the changes ensured that those items were more appropriate for use with a South African sample. The booklet that accompanies the CAMCOG-R (which contains pictures relating to some of the test items) was reprinted with more culturally appropriate images. (For details on specific changes, see Appendix B.)

Included in the CAMCOG-R are the 19 questions that comprise the *Mini-Mental State Examination* (*MMSE*; Folstein et al., 1975). The MMSE was used as a screening tool for dementia and for the detection of late-stage dementia, in accordance with the exclusion criterion of an MMSE score < 12. This instrument is the most commonly used and studied screening test for dementia. Despite controversies about its specificity and sensitivity, the MMSE has good test-retest and inter-rater reliability, and high construct validity (Strauss, Sherman, & Spreen, 2006). This measure has been used previously in a South African study investigating early-onset AD (Heckmann et al., 2004), and is used regularly as a screening tool for dementia in South African clinical practice.

The Placing Test (TPT; Anderson, de Jager, & Iversen, 2006) is a measure of implicit visual learning and memory. This instrument was developed as a tool for use in the early detection of AD. It assesses whether the testee can form associations between commonly-seen objects (for example, faces and shoes) and their location on the page of a stimulus booklet.

I showed participants two sets of five pages, with each page divided into four quadrants. On each page were two pictures; the first set of five pages featured two pictures of faces on each page, and the second set of five pages featured two pictures of shoes on each page. The location of the pictures on each page varied randomly. To control for encoding, participants were asked to judge whether the faces looked young or old, and whether the shoes would be worn by a man or a woman. After presentation of the pictures in each category, I showed participants the presented pictures one at a time and asked them to indicate where on the page (in one of the four quadrants numbered 1-4) they recalled seeing the picture.

Administration time for this test is 5-10 minutes, and performance is scored by the number of items placed correctly; hence, the maximum attainable score is 20. The fact that this is a non-verbal test renders it suitable for individuals whose first language is not English or who have a limited educational background. The test has been demonstrated to be free from the influence of education (de Jager, Hogervorst, Combrinck, & Budge, 2003), and has good discriminative capacity between controls and other groups with cognitive impairment (Anderson, de Jager, & Iversen, 2006). To my knowledge, test-retest reliability for this measure has not yet been formally established. Prior to this study, the TPT had not yet been administered to a South African sample in a published research study.

The *Trail Making Test* (*TMT*; Reitan & Wolfson, 1985) is a measure of motor speed, visuomotor tracking, visual attention, and switching ability (Lezak et al., 2004). This measure often forms part of neuropsychological screening batteries. The first part of the test (TMT-A) requires the testee to connect circled numbers in ascending numerical order. The second part of the test (TMT-B) requires the participant to connect numbers and letters in alternating order (i.e., 1-A-2-B-3-C, etc.).

Here, time taken to complete the task served as the performance measure. If the participant did not complete either TMT-A or TMT-B within 5 minutes, or if s/he was simply unable to meet the demands of the test, s/he was assigned a score of 300 seconds.

The TMT is sensitive to cognitive decline consistent with dementia (Kowalczyk, McDonald, Cranney, & McMahon, 2001), and is used often as a measure of how much an older adult might struggle with complex daily activities, such as driving (Stutts, Stewart, & Martell, 1998). This test has fairly good psychometric properties (Lezak et al., 2004), and is used frequently in South African clinical settings.

The *Executive Clock Drawing Task (CLOX;* Royall, Cordes, & Polk, 1998) provided an indicator of participants' executive and visuospatial performance. The first part of this task (CLOX 1) requires the participant to draw a clock with no help or cues from the examiner other than the following instructions: "Draw me a clock that says 1:45pm. Set the hands and numbers on the face so that a child could read them." CLOX 1 measures an individual's ability to perform in a novel situation; the focus is on executive (planning, executing, judging) and constructional abilities. The second part of the task (CLOX 2) requires the participant to copy a clock drawn by the examiner, and demonstrates visuospatial ability (Royall, Cordes, & Polk, 1998; Shon et al., 2013).

Scores for each part of the test range from 0-15. Each is scored separately, and an additional score can be calculated by subtracting scores for CLOX 1 from scores for CLOX 2. This latter score allows one to examine the contribution of executive control versus visuospatial praxis (Royall et al., 1998). The CLOX has good internal consistency and high inter-rater reliability (Strauss et al., 2006). This test has been used in studies focusing on the early detection of AD (e.g., Toepper, Beblo, Thomas, & Driessen, 2008), and is used for this purpose at the GSH Memory Clinic.

Physiological measures. I used *Sarstedt Salivette® Cortisol* devices to collect saliva samples for the determination of cortisol levels. These devices are composed of a cylindrical cotton sponge in a plastic holder fitted inside a centrifuge tube.

A research nurse drew *blood samples* from all participants after informed consent for this procedure (see Appendix C) had been obtained. These samples were used to perform APOE genotyping, and to determine plasma Aβ concentrations.

Structural MRI acquisition. All scans were performed by a radiographer using a 3-Tesla Siemens Allegra head scanner (Siemens Medical Systems, Erlangen, Germany). The individual imaging sequence that was relevant to the analysis was a T1-weighted MRI anatomical scan using a sagittal volumetric magnetization-prepared rapid gradient-echo. The acquisition parameters were as follows: slices = 160 contiguous slices; slice thickness = 1.3 millimetres (mm); resolution = 1.3x1.0x1.3 mm; recovery time (TR) = 2530 ms; field of view read = 256 mm; flip angle = 7 degrees; echo spacing = 8.9 ms; base resolution = 256; phase resolution = 75%; and bandwidth = 651 Hz/pixel. For the purposes of this study, I was especially interested in acquiring hippocampal volumes from the structural MRI datasets.

Procedures

Figure 5 shows a general outline of the entire study procedure. Members of the research team contacted participants either telephonically or via the care homes in which the participants resided. After initial contact, a member of the research team screened the participant telephonically to determine if s/he met the study's inclusion criteria. Those who were eligible were asked to give their initial verbal consent for participation. In the case of the possible or probable AD patients, the researcher also obtained consent from family members or legal guardians. Full details regarding ethical

considerations will be discussed later in this section under the heading *Ethical and Safety Considerations*.

During the same telephone call, the researcher arranged an appointment for the participant and an informant to attend a test session and a clinical visit in the Division of Neurology. The day before the test session, the researcher contacted the participant and/or the informant to remind them of their GSH visit.

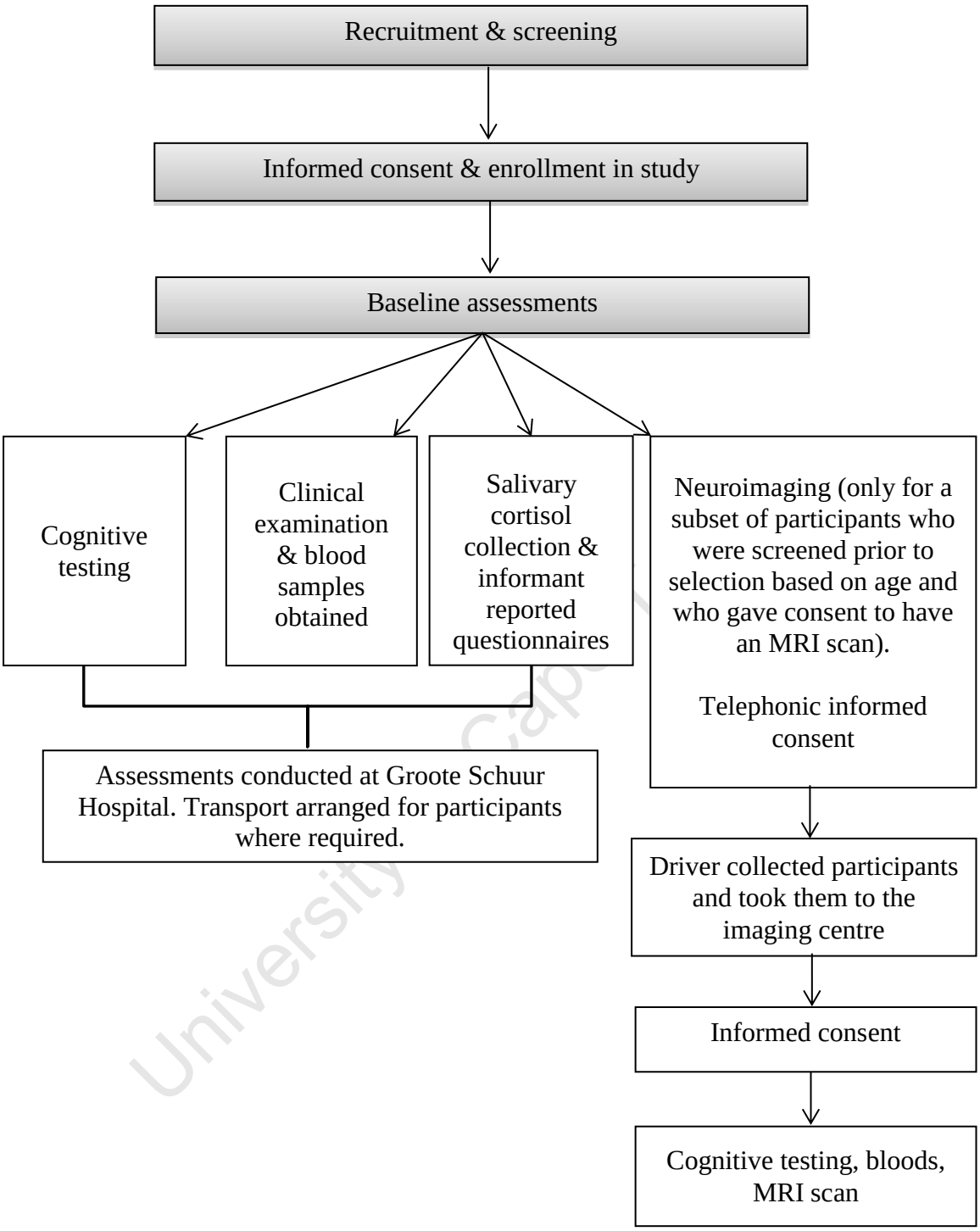


Figure 5. Flow chart of the procedures followed, including baseline collection of cognitive and physiological data and neuroimaging.

Clinical interview and neuropsychological testing. When the participant and informant arrived at GSH, they were met by the researcher and escorted to the testing venue in the Division of Neurology. The participant was provided with an information and consent document that provided full details of the study (Appendix C). Participants were provided with time to read through document, to ask questions, and to withdraw from participation if they so wished, without any prejudice for their future medical treatment. Participants who chose to continue were asked to sign the informed consent document before commencing testing procedures.

The first part of the test session involved the participant and informant completing the questionnaires described above (i.e., the sociodemographic questionnaire, the LTE-Q, PSS, DECO, BADLS, CD-RISC, and GDS). If an informant was not present, the relevant questionnaires were completed telephonically or electronically. Where the participant was not able to complete the self-report questionnaires by him/herself, the researcher assisted by reading the questions and filling in the participant's responses. After completion of the questionnaires, the researcher administered the neuropsychological test battery (i.e., CAMCOG-R, TPT, TMT, and CLOX). The interview and neuropsychological test session usually lasted between 1.25 and 2 hours. Participants were offered short breaks during this time.

At the end of the interview and testing session, the researcher provided the participant and/or the informant with two sets of salivettes and instructions for using them (see Appendix D). For those participants with memory problems, the instructions and salivettes were given to the informant, who was also instructed to assist the participant in obtaining the saliva sample. Participants were required to collect their saliva samples at 09h00 on two mornings in succession, within approximately one week of their cognitive assessment. Once both samples had been taken, the participant, or the informant, called the research team to let us know that the samples were ready for collection. After the researcher collected the salivettes, they were stored in a freezer at -20°C at GSH.

Immediately after the testing session, the research doctor performed the clinical exam and the research nurse took blood samples (maximum 36ml of blood taken), time permitting. Where there was insufficient time for all the assessments to be conducted on the same day, the clinical exam was performed at a subsequent visit a few days later. Either way, the clinical exam lasted between 1 and 2 hours.

Analytical procedures for saliva and blood samples. Once a batch of salivettes had been collected and stored in a freezer at -20°C, the researcher took them to the hospital's Chemical Pathology Laboratory, where a standard assay was performed to determine salivary cortisol levels.

Baseline blood samples taken at either the first cognitive testing session or at the subsequent clinical examination visit were sent immediately to a diagnostic chemical pathology laboratory for routine dementia screening blood tests, including renal, hepatic, thyroid function, vitamin B12, and syphilis serology tests. Samples for specific research tests were transported immediately and on ice to the research laboratory, where serum, plasma, and buffy coat were collected using a benchtop laboratory centrifuge machine.

The serum and plasma supernatants were aliquotted into individual polypropylene tubes to avoid the effects of repeated freeze/thaw cycles on potential assay parameters. The aliquotted samples were then stored in a -80°C freezer before being sent in batches to a pathology lab. Laboratory technicians extracted genomic DNA from the stored buffy coat layers. APOE genotype was determined using a standard method involving the polymerase chain reactions technique, as described by Hixson and Vernier (1990). The laboratory scientists who performed the APOE genotyping had no knowledge of the participants' demographic characteristics or of their clinical diagnoses. Furthermore, the researchers and clinicians were unaware of the genotype results when the diagnosis of possible or probable AD was given and when the neuropsychological exam was performed.

Regarding *plasma Aβ determinations*, 40 samples of 200µl undiluted human plasma samples, prepared from whole blood samples collected in EDTA-containing tubes, were stored at -80°C prior to analysis. Laboratory technicians used the Bio-Plex® 200 technology, based at a specialist laboratory at UCT's Faculty of Health Sciences, to determine the different forms of the plasma Aβ concentrations (Aβ1-42 and Aβ1-40) from these samples, using a commercially available fluorimetric bead-based immunoassay from INNOGENETICS (Ghent, Belgium). This was a 96-well assay kit called the Inno BIA Plasma Aβ Forms 96 Test. This assay allows for the simultaneous quantification of human Aβ forms in plasma. Calculations can then be performed of the ratios of the amounts of the different Aβ forms that are present in the sample, for example, Aβ1-42/1-40. The numbers 1-40 and 1-42 correspond to the length of the sequence of the Aβ peptide. The specialist laboratory performed the assay according to

the manufacturer's instructions. This kit required the use of 50µl of plasma, in duplicate for each participant, which was then diluted and run through the Bio-Plex system. For the test results, the laboratory technicians calculated the means of the median fluorescence intensity signal for the standards and unknown samples and constructed a standard curve. Using the mean signal value of each unknown plasma sample, they determined the corresponding concentration of each Aβ form from the relevant standard curve and then provided us with the detailed results.

Neuroimaging. A radiographer at the imaging centre performed the MRI scans. The latter provided the raw data for the determinations of brain hippocampal volumes. The methods used in the neuroimaging protocol were as follows: Only those participants who provided consent to have a brain scan, who were within the required age range (60-90 years), and/or where it was justified for diagnostic purposes, were included in this part of the study. Members of the research team (Katharine James and Laurian Grace, a fellow PhD researcher in the Faculty of Health Sciences at the University of Cape Town), in consultation with the radiographer, formally screened participants telephonically to determine whether or not they were suitable for scanning. This screening involved using a questionnaire (see Appendix E) that confirmed that the participant had not previously been a welder/metal grinder, and that s/he did not have any of the following: cardiac pacemaker, neurostimulator, eye trauma/foreign body, previous neurosurgery, previous surgery, cochlear implant, or claustrophobia.

Eligible participants were collected from either their place of residence or from GSH and taken to the imaging centre by a driver (an employee of the research team). On arrival, participants were asked to sign a consent form. This is the same form as that used for their screening; in other words the form that was used to assess their suitability for having an MRI scan. The radiographer confirmed that the participant did not have any contraindications for having a brain MRI scan. Following this, but prior to the scan itself, a researcher administered the MMSE and Learning subscale of the CAMCOG-R to the participants. These cognitive tests were performed so that the cognitive data would correspond in terms of time with the neuroimaging data. These specific tests were selected because (a) the MMSE has frequently been used as a measure of cognition in neuroimaging studies of the hippocampus (Slavin, Sandstrom, Tran, Doraiswamy, & Petrella, 2007; Steffens, McQuoid, Payne, & Potter, 2011; Vijayakumar & Vijayakumar, 2012), and (b) the Learning subscale provides an approximate measure of new learning and memory which are key features of

hippocampal functioning (Eichenbaum, 2003; Cipolotti et al., 2001). The research nurse drew blood samples (these blood samples were taken as part of a co-researcher's project). Participants then changed into a hospital gown.

The radiographer then took each participant into the scanner room and asked him/her to lie down on the scanning table. The radiographer provided the participant with an emergency button, and she explained how and when to use it. She gave each participant earplugs (to reduce the noise of the scanner) as well as MRI-compatible headphones (to enable communication between the participant and the radiographer and for music to be played to the participant). Lastly, the radiographer placed foam padding around the participant's head within the head cradle for head stabilization, and she instructed participants to lie as still as possible and to avoid head movements during the scanning procedure.

The table on which the participant was lying was then moved into the scanning machine for the 28-min duration of the scan. The scanning procedure included the acquisition of magnetic resonance spectroscopy data, which were collected for another study. The duration of the scan specifically for the acquisition of the localization and structural MRI data was 8:06 min.

MRI automated analyses. I performed automated analyses of the MRI data using the Freesurfer image analysis suite (version 4.5; see http://surfer.nmr.mgh.harvard.edu/). This software provided reliable automated measurements of total intracranial volume (ICV), which would be too time-consuming to determine manually, but which corresponds well with manual measurements (Buckner et al., 2004). The Freesurfer software was also used for the automated parcelation and segmentation of all brain regions. Reconstructions of these images were run on an Intel Nehalem cluster at the Centre for High Performance Computing in Cape Town (http://www.chpc.ac.za).

The automated image processing for cortical reconstruction and volumetric segmentation used in this study included the automated Talairach transformation, segmentation of the subcortical deep grey matter volumetric structures such as the hippocampi (Fischl et al., 2002; Fischl et al., 2004a), intensity normalization (Sled, Zijdenbos, & Evans, 1998), tessellation of the grey matter white matter boundary, and automated topology correction (Fischl, Liu, & Dale, 2001; Segonne, Pacheco, & Fischl, 2007). More extensive details relating to the Freesurfer technical procedures can be found elsewhere (Dale, Fischl, & Sereno, 1999; Fischl & Dale, 2000; Fischl, et al.,

2001; Fischl, 2002; Fischl et al., 2004a; Han et al., 2006; Segonne et al., 2004; Fischl, 2012).

Within the Freesurfer software program, I used TKMedit which allowed me to review the image data with a display of anatomical volumes in different orientations. This review enabled me to verify all reconstructions individually and across different slices and planes. Where necessary, I manually corrected the Talairach transformation, the skull stripping, and the white matter and pial edits within Freesurfer. The corrected images were then submitted to the Intel Nehalem cluster for reconstruction. Inspection and reconstruction of the images was supervised by an independent consultant from CUBIC who has specialist knowledge and expertise in neuroimaging and in use of the Freesurfer software. The consultant was blind to group status of the images and had no knowledge of the study hypotheses.

MRI manual analyses. This study employed a manual technique for the structural MRI analysis of hippocampal volume. To prepare the MRI images for manual analysis, I used Brain Voyager QX, version 2.0 (Brain Innovation B.V., Maastricht, Netherlands). I first checked that the images were iso-voxeled, then rotated them into the anterior-commissure–posterior-commissure plane, and normalised them to the standard Talairach anatomical brain template for the purpose of between-group analyses. After taking those steps, I exported the images to the Analyze format for manual tracing.

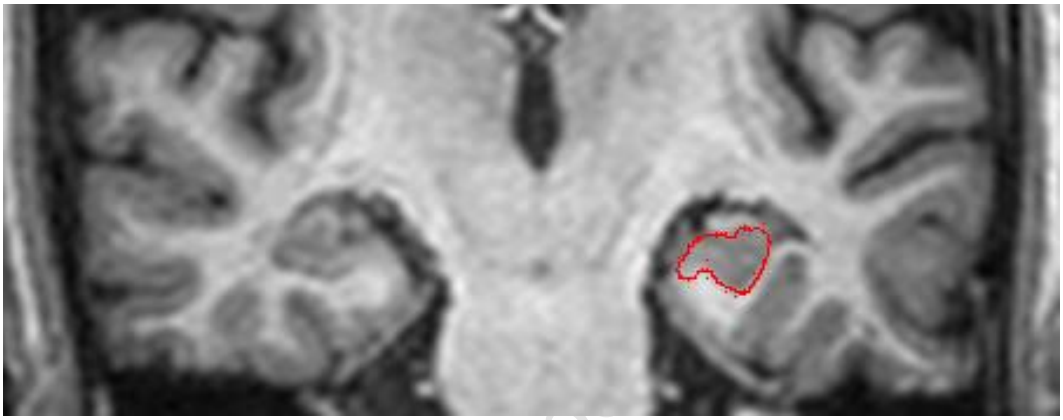
I performed the manual tracing using MultiTracer, version 1.0 (Woods, 2003) from the Laboratory of Neuro Imaging, University of California, Los Angeles. I magnified the images 6 times and traced them on a laptop tablet with an LED screen, using a stylus pen.

I traced the hippocampal volumes manually, with the assistance of an experienced neuroanatomist, using the same type of tablet at the same level of magnification. This method provided accurate volumetric measurements of the hippocampus, specifically. As mentioned above, I also used Freesurfer software to determine total ICV, from which I then adjusted the hippocampal volumes.

I traced the hippocampal structures in both the sagittal and coronal planes to enhance viewing accuracy; only the coronal tracings were used to calculate hippocampal volumes, however (see Figure 6). I defined and traced the hippocampus including the head, body, and tail, the dentate gyrus, and part of the subiculum. I used the alveus as a marker between the hippocampus and the amygdala. I drew within the

inner boundary of the alveus to exclude it, and, where visible, I used the CSF and lateral ventricle as supplementary landmarks. I excluded the fimbria and the fornix from the tracings. I also used the superior medial edge of the temporal lobe white matter as the medial boundary, drawing a line at 90° to the cortical surface, to demarcate the junction of the hippocampal formation with the parahippocampal gyrus.

A



B

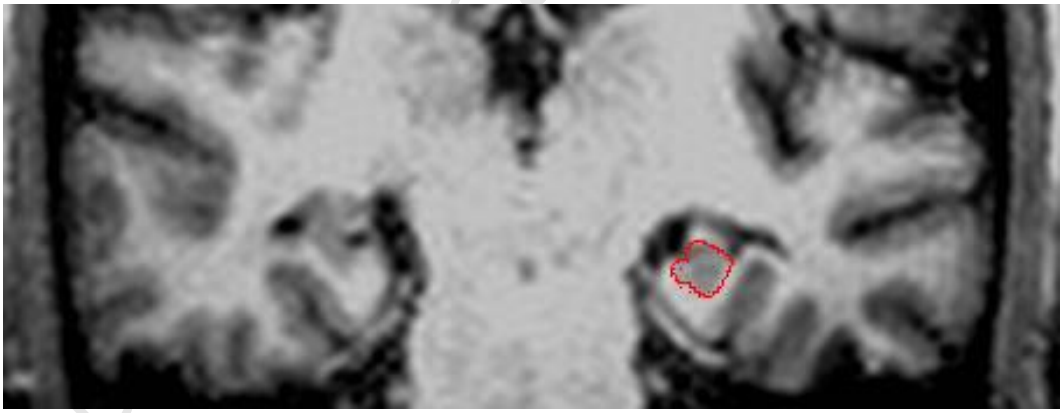


Figure 6. Coronal view of the anatomic borders of the left hippocampus, outlined in red, on MRI. Selected images from (A) a 69-year-old male control participant, and (B) a 69-year-old male AD patient.

Blind to participant group status and demographic variables, I traced the hippocampi of all the participants and captured their frust volume measurements. (The frust volume is the volume calculated by assuming that the structure extends from the centre of the first plane on which it was drawn to the centre of the last plane on which it was drawn, with the square root of areas varying linearly when moving from the centre of one plane to the centre of the next; (Woods, 2005)).

One month later, I retraced the hippocampi of 10 brains. To assess my self-consistency, I calculated intra-rater reliability using a two-way ANOVA (N = 10), mixed-effects model Intraclass Correlation Coefficient (ICC) test to evaluate the degree of agreement between my first and second tracings. The ICC demonstrated that I had good intra-rater reliability, with an average measure's ICC value of .993, $p < .001$ and a single measure's ICC of .986, $p < .001$ for the left hippocampi, and an average measure's ICC value of .987, $p < .001$ and a single measure's ICC of .974, $p < .001$ for the right hippocampi. The single measure ICC indicates the reliability of the individual raters, while the average measure ICC relates to the reliability of the mean of the ratings. Also blinded to participant group status and demographic variables, the neuroanatomist traced hippocampi from 10 scans to determine the reliability of my tracings (i.e., to measure how similar my hippocampal volumetric measurements were with his). We achieved strong inter-rater reliability, with an average measure's ICC value of .965, $p < .001$, and a single measure's ICC of .932, $p < .001$ for the right hippocampi.

Ethical and Safety Considerations

All study procedures were approved by the Research Ethics Committees of the University of Cape Town's Department of Psychology and the Faculty of Health Sciences (REC REF 346/2008). This study was conducted according to the ethical guidelines and principles stated in the International Declaration of Helsinki, the South African Guidelines for Good Clinical Practice, and the South African Medical Research Council (MRC) Ethical Guidelines for Research.

All participants were provided with thorough and detailed written and verbal information about the study (Appendix D); their anonymity was assured and they were informed of their right to withdraw from the study at any given point. Participants were informed about all the relevant study procedures and what their role in the study would entail.

Ethical approval for the neuroimaging study was granted in a protocol amendment document (REC REF 346/2008, Amendment 2012). Regarding participation in the neuroimaging component of the study, these participants were provided with a separate consent form and were informed about any possible risks. The facility where the scanning procedure took place is a well-equipped centre with highly

qualified staff members who ensured that all the necessary MR safety protocols were adhered to strictly.

Prior to commencement of the scanning procedure, participants were provided with hospital robes to wear in the scanner. During the scan itself, participants were able to close their eyes, listen to music, or rest. If necessary, participants were able to talk to the study doctor/assistant/radiographer at any time. We bore in mind that, because the scan was done in a relatively confined space, some people might have become claustrophobic. This did not occur often, however, and where any of the participants did feel anxious, a study representative gave them time to get used to the surroundings before scanning began. In a small number of cases, the participants became very anxious and elected not to proceed with the scan. In those cases (n = 5), the scan was terminated prematurely. The participants who withdrew thus were four female AD patients (67, 70, 79, and 83 years old respectively), and one female control (74 years old).

Statistical Analyses

I sorted and cleaned the data and checked for any missing items. I performed all analyses using Statistica 10 or SPSS version 19.0. I performed descriptive statistical analyses for all the data and calculated measures of central tendency (mean and median) and dispersion (range, standard deviation, and variance) for all variables. I also constructed boxplots for all the continuous independent variables in order to detect outliers that may have influenced the measures of central tendency. For all of these analyses, the alpha level was set at .05. I used Cohen's d or partial eta squared (η_p^2) as estimates of the effect sizes for parametric data. To calculate effect sizes for non-parametric data, I used Cohen's r. Cohen defines the effect size ranges as 0.2 = small effect, 0.5 = medium effect, 0.8 = large effect (Cohen, 1988).

For some of the factors of interest, I performed exploratory analyses that were not a direct part of any of the *a priori* hypotheses, but which the literature indicated might be worthwhile. I present the results of those exploratory analyses at the end of each relevant section, after presentation of the hypothesis-driven results.

Demographic, neuropsychological, affective, and behavioural data. To examine between-group differences in sociodemographic variables and in measures of

current neuropsychological, affective, and behavioural functioning, I used independent-samples *t*-tests or Mann-Whitney *U*-tests.

Current psychosocial stress, lifetime trauma, and current cortisol levels. As noted above, the PSS is a measure of current perceived stress, and was used here as a measure of psychosocial stress because it relates to everyday stressors. I decided to use only the PSS, which looks at recent acute stressors likely to occur in daily life, as a measure of psychosocial stress, rather than using a composite of the PSS and LTE-Q. I made this decision because research suggests that daily life stressors, rather than major life events which are relatively rare, have a cumulative and perhaps more severe effect on well-being (Zautra, Affleck, Tennen, Reich, & Davis, 2005; Almeida, Neupert, Banks, & Serido, 2005) Scores on the PSS and LTE-Q were weakly correlated with each other, $r(132) = .29$, $p < .001$, but the instruments do not measure the same construct(s); thus, creating a composite variable might have conflated constructs.

As noted above, the LTE-Q provides scores for recent stress (traumatic events experienced < 6 months ago) and remote stress (traumatic events experienced > 6 months ago). Hence, from here onwards, the variable names *recent stress* and *remote stress* refer to those separate LTE-Q scores. The sum of those separate LTE-Q scores produced a total LTE-Q score (i.e., the *lifetime stress* variable). To test hypotheses related to psychosocial stress and lifetime traumatic events (*Hypothesis 1a*, as listed above), I examined between-group differences using either independent samples *t*-tests or Mann Whitney *U*-tests.

Pearson product-moment correlation analyses assessed the associations between psychosocial stress and current cortisol levels (*Hypothesis 1b*), between psychosocial stress and cognition, and between cortisol and cognition (*Hypothesis 1c*). I derived a single measure of circulating cortisol for each participant by averaging the two morning salivary cortisol readings from each. The cortisol measurements are in nanomoles per litre (nmol/L). These baseline raw scores for cortisol levels were not normally distributed, and so the appropriate nonparametric tests were used in analyses of this variable. Regarding the measure of cognition used in the abovementioned correlations, there were three: CAMCOG-R Total score, MMSE score, and CAMCOG-R Learning subscale score. Furthermore, I performed a correlational analysis to determine if cortisol was related to age, in which case I would need to control for age in the cortisol analyses. I also performed a *t*-test to examine between-group differences for cortisol levels.

Resilience. Correlational analyses assessed the associations between levels of resilience and psychosocial stress (*Hypothesis 2a*), and between levels of resilience and years of education (*Hypothesis 2b*).

Apolipoprotein ϵ4. After calculating descriptive statistics to determine the frequency of APOE-ϵ4 in each group, I conducted a chi-square (χ^2) test of contingency to assess between-group differences in terms of APOE-ϵ4 frequency (*Hypothesis 3a*). Due to the limited number of APOE-ϵ4 homozygotes (n_{HC} = 2, n_{AD} = 9) in this sample, I divided participants into two groups for APOE-ϵ4: those with the ϵ4 allele, ϵ4 carriers (ϵ4+), and those without the ϵ4 allele, ϵ4 non-carriers (ϵ4-). I then conducted *t*-tests to determine differences in cognition (CAMCOG-R score) within each group (*Hypothesis 3b*). I also ran *t*-tests to determine if levels of psychosocial stress and cortisol were higher in controls and AD patients with APOE-ϵ4 than in those without APOE-ϵ4. To assess whether AD patients with higher levels of psychosocial stress and the presence of the ϵ4 allele performed more poorly on the CAMCOG-R than AD patients with lower levels of psychosocial stress and an absence of APOE-ϵ4 (*Hypothesis 3c*), I performed a univariate ANOVA. For this analysis, the total CAMCOG-R score was the dependent variable and psychosocial stress, defined by a median split (high:low) and APOE-ϵ4 (with:without) were entered as fixed factors. Finally, to examine whether AD patients with higher baseline cortisol levels and the presence of the ϵ4 allele performed more poorly on the CAMCOG-R than AD patients with lower baseline levels of cortisol and an absence of APOE-ϵ4 (*Hypothesis 3d*), I performed a univariate ANOVA. For this analysis, the total CAMCOG-R score was the dependent variable and cortisol, defined by a median split (high:low) and APOE-ϵ4 (with:without) were entered as fixed factors.

Beta-amyloid. I used *t*-tests to determine whether there were between-group differences in plasma Aβ levels (Aβ1-42, Aβ1-40, and Aβ1-42/Aβ1-40 ratio; Hypothesis 4a). To determine whether AD patients with high levels of psychosocial stress had lower levels of plasma Aβ than AD patients with low levels of psychosocial stress (*Hypothesis 4b*), I created a median split for psychosocial stress and performed a *t*-test. To determine whether AD patients with high levels of cortisol had lower levels of plasma Aβ than AD patients with low levels of cortisol, I created a median split for cortisol and performed a *t*-test.

Hippocampal volume. I determined left and right hippocampal volumes in each participant using the manual tracing method described above. Hippocampal volumes

are presented in cubic millimetres (mm^3). I then summed and divided the hippocampal volumes by each participant's total ICV to control for intersubject variation in brain size, in accordance with previous volumetric analyses (Basso et al., 2006; Knoops, Gerritsen, van der Graaf, Mali, & Geerlings, 2012). The size of hippocampi can vary proportionally to ICV, and structural analysis of brain regions is challenged by the fact that brain size can vary markedly among individuals (Buckner et al., 2004). Measurements of ICV are independent of atrophy and can be used safely to adjust for premorbid brain and head size in studies of cerebral structures in AD (Jenkins, Fox, Rossor, Harvey, & Rossor, 2000).

I conducted Pearson product-moment correlations to examine associations between age and ICV, between disease status (as measured by MMSE scores in the AD patient group) and ICV, between adjusted hippocampal volume (right, left, and total) and cortisol levels, and between hippocampal volume (right, left, and total) and cognitive performance. I performed *t*-tests to examine whether AD patients had smaller hippocampal volumes than controls (*Hypothesis 5a*).

To test whether AD patients with high baseline cortisol levels (defined by a median split) and the presence of the APOE-ϵ4 allele had smaller hippocampal volumes than patients with low baseline cortisol levels and without APOE-ϵ4 (*Hypothesis 5b*), I performed a univariate ANOVA with total adjusted hippocampal volume as the dependent variable and cortisol defined by a median split (high:low) and APOE-ϵ4 (with:without) as the fixed factors.

Multiple regression model. Initially, I intended to explore my data using a structural equation model (SEM) which would have allowed for the simultaneous investigation of the relationships between age, education, resilience, APOE-ϵ4, cortisol, psychosocial stress, and cognition. Unfortunately, preliminary analyses indicated that the SEM was not going to be a feasible technique for analyzing these data. For instance, some of the variables that should not have been correlated with each other, for the purposes of the SEM, were highly correlated (see Table F1 in Appendix F for details of these preliminary results).

As a reasonable alternative to using a SEM, I performed a hierarchical multiple regression to investigate which factors were significant predictors of cognition. The following independent variables (selected based on the literature) were entered into the model one by one, in this order: age, education, APOE-ϵ4, cortisol, and psychosocial stress. Resilience was not entered as a variable in this model because of its high

collinearity with psychosocial stress. The outcome variable (i.e., the measure of cognitive functioning) was CAMCOG-R Total Score.

Results

Results for Study 1 are grouped and presented in order of their related hypotheses. Results for the five sets of hypotheses are presented first, followed by the results for the regression model. For some variables (viz., psychosocial stress, lifetime trauma, current cortisol levels, APOE-ϵ4, and Aβ), I performed exploratory analyses. These analyses were not related directly to the hypotheses, but I report them here because they might be of interest in that they relate to data reported in previously published studies. Therefore, in the exploratory analyses sections, I refer briefly to relevant studies to place those analyses in the context of the literature.

Demographic, Neuropsychological, and Behavioural Data

Table 2 presents the sample's demographic data. On average, controls were significantly younger than AD patients and had more years of education. Most participants in both groups were female. Although AD patients had, on average, a slightly lower body mass index (BMI) than controls, there were no significant between-group differences in this regard; hence, this variable should not have influenced between-group differences in cortisol levels. In terms of SES status, most controls had a monthly household income of more than ZAR2500 (approximately US$250, at the time of this study), whereas most AD patients had a monthly household income of less than that.

Table 2
Sample Demographic Data at Baseline (N = 134)

Variable	Group: Controls (*n* = 69)	Group: AD Patients (*n* = 65)	*df*	t / χ^2	*p*	ESE
Age	71.03 (8.72)	76.49(7.92)	133	-.3.79[a]	< .001***	0.66
Sex (M:F)	16:53	22:43	1	1.87[b]	.17	-0.12
Race (W:B:C:I)	43:1:25:0	13:1:49:2	3	25.76[b]	.001***	0.44
Education (years)	13.81 (4.68)	9.32 (3.13)	133	6.49[a]	.001***	1.11
Handedness (Right:Left)	62:7	61:4	1	0.71[b]	.40	0.07
Body Mass Index	27.40 (6.05)	25.57 (5.11)	107	1.69[a]	.09	0.33
Income						
< ZAR2500:≥ ZAR2500	13:56	50:15	1	45.33	< .001***	0.58

Note. For the variables *Age*, *Education*, and *Body Mass Index*, means are presented with standard deviations in parentheses. For the variable *Race*, W = White, B = Black African, C = Coloured, I = Indian. (This classification of race groups is in line with historical classification of the dominant population groups in South Africa, and with current census classification practice; it is reported here purely as a means to characterize the sample). The variable *Income* refers to monthly household income; all units of currency in this study are ZAR = South African Rand. [a]Test statistic for *t*-test. [b]Test statistic for Mann-Whitney U test. ESE = effect size estimate; in this case, either Cohen's *d* (for *t*-tests) or phi (φ) (for χ^2 tests).
*p < .05. **p < .01. ***p < .001.

Table 3 presents descriptive statistics for the cognitive and behavioural measures at baseline. AD patients had significantly poorer affective, behavioural, and adaptive functioning compared to the controls. Although the analyses presented in the Table did not control for the significant between-group differences in terms of age and education (see Table 2), the influence of education and age on cognitive functioning are examined in the regression models presented later. Of note here, though, is that, across the entire sample, age was significantly correlated with CAMCOG-R total score; with increasing age, CAMCOG-R scores decreased, $r(133) = -0.38$, $p < .001$. Similarly, across the entire sample, education was significantly correlated with CAMCOG-R total score; with increasing education, $r(133) = -.57$, $p < .001$. There was no significant sex difference in CAMCOG-R Total Score (men: $M = 80.71$, $SD = 14.00$; women: $M = 79.05$, $SD = 18.13$), $t(131) = 0.51$, $p = .61$.

Table 3

Descriptive Statistics for Cognitive and Behavioural Measures at Baseline (N = 134)

		Group						
		Controls (n = 69)		AD Patients (n = 65)				
Variable	Max. Attainable Score	*M* (*SD*)	Median (IQR)	*M* (*SD*)	Median (IQR)	*t* / *Z*	*p*	ESE
CAMCOG-R	105	92.52 (5.21)	94.00 (7.00)	65.38 (13.78)	68.00 (20.00)	15.36[a]	< .001***	2.61
Memory	27	21.36 (2.12)	21.00 (3.00)	10.94 (5.22)	10.00 (8.00)	9.47[b]	< .001***	0.82
Orientation	10	9.77 (0.55)	10.00 (0.00)	6.89 (2.44)	7.00 (4.00)	7.25[b]	< .001***	0.63
Language	30	27.13 (1.55)	27.00 (1.00)	23. 35 (3.08)	24.00 (5.00)	7.81[b]	< .001***	0.67
Attention	7	6.28 (0.55)	7.00 (1.00)	4.17 (2.24)	4.00 (4.00)	5.81[b]	< .001***	0.50
Calculation	2	1.20 (0.35)	2.00 (0.00)	1.42 (0.66)	2.00 (1.00)	4.05[b]	< .001***	0.35
Praxis	12	11.22 (0.89)	11.00 (1.00)	9.07 (2.24)	9.00 (3.00)	6.14[b]	< .001***	0.53
Abstract Thinking	8	6.91 (1.09)	7.00 (2.00)	4.12(2.34)	5.00 (4.00)	7.52[b]	< .001***	0.65
Perception	9	7.87 (1.24)	8.00 (2.00)	5.45 (1.72)	5.00 (2.00)	9.43[a]	< .001***	1.61
MMSE	30	28.14 (2.36)	29.00 (2.00)	20.80 (5.10)	22.00 (6.00)	8.95[b]	< .001***	0.77
Learning	17	14.00 (2.40)	14.00 (2.00)	7.51 (3.85)	8.00 (6.00)	8.88[b]	< .001***	0.77
GDS	15	1.70 (2.32)	1.00 (2.00)	2.60 (2.22)	2.00 (3.00)	-2.99[b]	0.002**	-0.26
BADLS	60	0.33 (1.30)	0.00 (0.00)	8.02 (6.80)	7.00 (11.00)	-7.82[b]	< .001***	-0.67
DECO	38	35.90 (3.48)	38.00 (4.00)	23. 50 (8.67)	23.50 (12.50)	7.72[b]	< .001***	0.66
CD-RISC	100	80.26 (12.71)	82.00 (17.00)	66.58 (12.67)	67.00 (16.00)	6.26[a]	< .001***	1.08

Note. Means (*M*) are presented with standard deviations (*SD*) in parentheses. Raw score medians are presented with interquartile ranges (IQR) in parentheses. CAMCOG-R = Cambridge Cognitive Examination-Revised; MMSE = Mini-Mental State Examination; GDS = Geriatric Depression Scale; BADLS = Bristol Activities of Daily Living; DECO = Deterioration Cognitive Observee. For each between-group comparison, degrees of freedom = 133, except for BADLS (120) and DECO (118). [a]Test statistic for *t*-test. [b]Test statistic for Mann-Whitney *U* test. ESE = effect size estimate; in this case, Cohen's *d* (for parametric data) or Cohen's *r* (for non-parametric data).

*p < .05. **p < .01. ***p < .001.

Table 4 presents between-group comparisons of neuropsychological test scores at baseline. AD patients performed more poorly than controls across measures of visuoconstructional ability (CLOX 2), planning and organization in addition to visuoconstructional ability (CLOX 1), visual attention and processing speed (TMT-A), cognitive switching in addition to visual attention and processing speed (TMT-B), and visual associative memory (TPT).

Table 4
Between-Group Comparisons: Neuropsychological test scores at baseline (N =134)

	Group				
	Controls (*n* = 69)	AD Patients (*n* = 65)			
Test variable	Median (IQR)	Median (IQR)	*Z*	*p*	ESE
TPT (total score)	16.00 (5.00)	7.00 (5.00)	7.52	< .001***	0.65
TMT-A	43.50 (19.00)	88.00 (66.00)	-7.34	< .001***	-0.63
TMT-B	100.00 (45.00)	300.00 (124.00)	-8.10	< .001***	-0.70
CLOX 1	13.00 (2.00)	11.00 (4.00)	6.56	< .001***	0.57
CLOX 2	14.00 (2.000	13.00 (3.00)	5.60	< .001***	0.48

Note. Medians are presented with interquartile ranges in parentheses. TPT = The Placing Test; TMT-A = Trail Making Test (Part A); TMT-B = Trail Making Test (Part B); CLOX 1 = Executive Clock Drawing Task (Part 1); CLOX 2 = Executive Clock Drawing Task (Part 2). For both TMT trials, the outcome variable is time, in seconds. For each between-group comparison, degrees of freedom = 132.
**p* < .05. ***p* < .01. ***p < .001.

Hypotheses Set 1: Psychosocial Stress, Lifetime Trauma, and Current Cortisol Levels

This group of results relates to this study's first set of hypotheses (viz., *Hypotheses 1a, 1b,* and *1c*). Table 5 presents results of the between-group comparisons regarding perceived current psychosocial stress, lifetime experiences of stress (recent and remote stress), and baseline cortisol levels.

Partially confirming *Hypothesis 1a*, mean PSS scores for patients (*n* = 65) were significantly higher than those for controls (*n* = 69); on the PSS, higher scores indicate greater perceived stress. PSS scores, however, were not influenced by disease severity, as measured by the AD patients' scores on the MMSE, $r(63) = -.02$, $p = .89$.

Partially disconfirming *Hypothesis 1a,* there were no significant between-group differences in terms of total LTE-Q scores (in fact, controls had, on average, slightly higher levels of total stress, as well as slightly higher levels of remote stress). Also partially disconfirming *Hypothesis 1a,* controlling for age, there were no significant between-group differences in terms of mean salivary cortisol levels (on average, AD patients had only slightly higher mean cortisol levels than controls).

The analyses did not confirm *Hypothesis 1b* (viz., that there would be a larger positive association between psychosocial stress and cortisol levels among AD patients than among controls): For patients, $r(63) = -.09$, $p = .45$, whereas for controls $r(67) = .03$, $p = .81$.

Similarly, the analyses did not confirm *Hypothesis 1c* (viz., that levels of psychosocial stress and cortisol would be negatively correlated with cognitive performance); see Table 6 for the results of these analyses within each group separately. The relationships between psychosocial stress and cortisol with cognition across the entire sample are explored in the multiple regression model discussed later in this section.

Exploratory analyses. There were no significant between-group differences in terms of LTE-Q measures of recent, remote, or total stress (Table 5). Furthermore, none of the three LTE-Q outcome variables correlated significantly with scores on any of the cognitive measures (CAMCOG-R, MMSE, or Learning score).

Regarding sex differences on the in psychosocial stress, previous studies suggest that healthy women experience their lives to be more stressful than healthy men do and that women achieve higher scores on the PSS than men (Cohen & Janicki-Deverts, 2012; Matud, 2004). This sex difference was confirmed in the current sample of healthy controls: Women ($n = 53$, $M = 19.00$, $SD = 8.48$) had significantly higher PSS scores than men ($n = 16$, $M = 13.06$, $SD = 6.72$), $t(67) = -2.56$, $p = .01$, $d = 1.01$. In the AD patient group, however, men ($n = 22$, $M = 24.27$, $SD = 7.12$) had significantly higher PSS scores than women ($n = 43$, $M = 19.93$, $SD = 7.67$), $t\ (63) = 2.21$, $p = .03$, $d = .59$.

An association between education and psychosocial stress has also been reported: Better-educated adults have been found to have less psychological stress (Grzywacz, Almeida, Neupert, & Ettner, 2004). In the current sample, there was a trend for higher levels of education to be associated with lower levels of psychosocial stress, as measured by the PSS, $r(133) = -.15$, $p = .08$.

Cortisol levels are known to increase with age, particularly in older adults (Zhao et al., 2003). In this sample, however, morning cortisol levels were not associated significantly with age in the AD patient group, $r(63) = .18$, $p = .16$. However, cortisol was associated with age in the control group, $r(67) = .36$, $p = .003$. Sex differences in salivary cortisol have also been reported previously (Larsson, Gullberg, Rastam, & Lindblad, 2009). In this sample, however, there was no statistically significant between-sex difference in cortisol levels (men, $n = 38$, $M = 9.11$, $SD = 15.39$; women, $n = 96$, $M = 10.96$, $SD = 19.68$), $t(144) = 0.55$, $p = .58$, $d = 0.11$.

Table 5

Between-Group Comparisons: Psychosocial and physiological stress at baseline (N = 134)

	Group						
	Controls (n = 69)		AD Patients (n = 65)				
Type of Stress	*M* (*SD*)	Median (IQR)	*M* (*SD*)	Median (IQR)	*t* / *Z*	*p*	ESE
LTE-Q							
Total stress	12.64 (6.60)	12.00 (9.00)	11.89 (7.60)	10.50 (7.00)	0.61[a]	.55	0.11
Remote stress	10.42 (5.50)	10.00 (8.00)	9.57 (5.29)	9.00 (7.00)	0.91[a]	.36	0.16
Recent stress	2.21 (2.79)	2.00 (3.00)	2.32 (4.52)	0.00 (3.00)	1.10[b]	.27	0.03
PSS	17.63 (8.45)	17.00 (10.00)	21.40 (7.71)	21.00 (10.00)	-2.70[a]	.01[*]	0.47
Cortisol	0.80 (0.31)	0.79 (0.35)	0.82 (0.33)	0.85 (0.52)	-0.31[a]	.76	0.06

Note. LTE-Q = List of Threatening Life Events Questionnaire. PSS = Perceived Stress Scale. Cortisol is measured in nmol/L. [a]Test statistic for *t*-test. [b]Test statistic for Mann-Whitney U test. ESE = effect size estimate (in this case, Cohen's *d* for parametric data and Cohen's *r* for non-parametric data). For each between-group comparison, degrees of freedom = 132, except for cortisol (115).

*$p < .05$.

Table 6
Correlations: Cognition, psychosocial stress, and cortisol at baseline (N = 134)

	Group			
	Controls (n = 69)		AD Patients (n = 65)	
	PSS	Cortisol	PSS	Cortisol
CAMCOG-R	.05	-.18	.04	.06

Note. Values presented are for Pearson's *r*. PSS = Perceived Stress Scale – measure of psychosocial stress. Cortisol = log transformed salivary cortisol levels. CAMCOG-R = Cambridge Cognitive Examination-Revised.

Hypotheses Set 2: Resilience

Hypotheses 2a and *2b* related to resilience and education and how they are associated with each other in both controls and AD patients. Confirming *Hypothesis 2a*, there was a statistically significant inverse relationship between resilience, as measured by the CD-RISC, and psychosocial stress, as measured by the PSS, in controls, $r(67) = -.46$, $p < .001$, in AD patients, $r(64) = -.28$, $p = .02$, and in the entire sample, $r(133) = -.43$, $p < .001$.

The analyses did not confirm *Hypothesis 2b*, however. There was no significant association between resilience, as measured by the CD-RISC, and number of years of formal education in either controls, $r(67) = .18$, $p = .15$, or AD patients, $r(64) = .04$, $p = .76$. In the entire sample, however, there was a significant positive association between resilience and education, $r(133) = .31$, $p < .001$.

Hypotheses Set 3: Apolipoprotein ϵ4

Confirming *Hypothesis 3a*, AD patients (n = 64) had a significantly higher ϵ4 allelic frequency than controls (n = 65), $\chi^2(127) = 9.25$, $p = .002$. The ϵ4 allelic frequency in the control group was 0.20, in the AD patient group it was 0.35, and in the entire sample it was 0.28. The ϵ3 allelic frequency in the control group was 0.70, in the AD patient group it was 0.56, and in the entire sample it was 0.63. The ϵ2 allelic frequency in the control group was 0.10, in the AD patient group it was 0.08, and in the entire sample it was 0.09.

Previous work has suggested that the presence of APOE-ϵ4 may modify the association between salivary cortisol levels and cognitive function (Gerritsen, Comijs, Deeg, Penninx, & Geerlings, 2010). Similar findings have been reported for

psychological stress (Peavy et al., 2007). In light of these findings, *Hypotheses 3b* and *3c* involved the relationship of APOE-ϵ4 to psychosocial stress, physiological stress, and cognition. *Hypothesis 3b* was not confirmed: Performance on the CAMCOG-R in AD patients with APOE-ϵ4 (n = 37, M = 65.24, SD = 14.16) did not differ significantly from performance on the CAMCOG-R in AD patients without ϵ4 (n = 27, M = 66.43, SD = 13.81), $t(63) = 0.34$, $p = .74$, $d = 0.09$.

In terms of *Hypothesis 3c*, the mean scores appeared to indicate that AD patients with high levels of psychosocial stress (as defined by a median split) and presence of the ϵ4 allele performed more poorly on the CAMCOG-R (n = 33, M = 61.38, SD = 13.73) than did AD patients with lower levels of psychosocial stress and absence of the ϵ4 allele (n = 32, M = 66.45, SD = 13.99). However, a univariate ANOVA found no main effect for APOE-ϵ4, $F(3, 60) = .00$, $p = .99$, $\eta_p^2 < .001$; no main effect for psychosocial stress, $F(3, 60) = 1.33$, $p = .25$, $\eta_p^2 = .02$; and no significant interaction between APOE-ϵ4 and psychosocial stress, $F(3, 60) = 2.76$, $p = .10$, $\eta_p^2 = .04$.

In terms of *Hypothesis 3d*, the mean scores depicted in Figure 7 appear to indicate that AD patients with high baseline cortisol levels (as defined by a median split) and presence of the ϵ4 allele (ϵ4+) performed more poorly on the CAMCOG-R (n = 30, M = 61.38, SD = 13.73) than did AD patients with low baseline cortisol levels and absence of the ϵ4 allele (ϵ4-; n = 10, M = 66.45, SD = 13.99). However, a univariate ANOVA found no main effect for APOE-ϵ4, $F(3, 61) = 0.02$, $p = .88$, $\eta_p^2 = .00$; no main effect for cortisol, $F(3, 61) = 1.49$, $p = .23$, $\eta_p^2 = .02$; and no significant interaction between APOE-ϵ4 and cortisol, $F(3, 61) = 1.44$, $p = .24$, $\eta_p^2 = .02$.

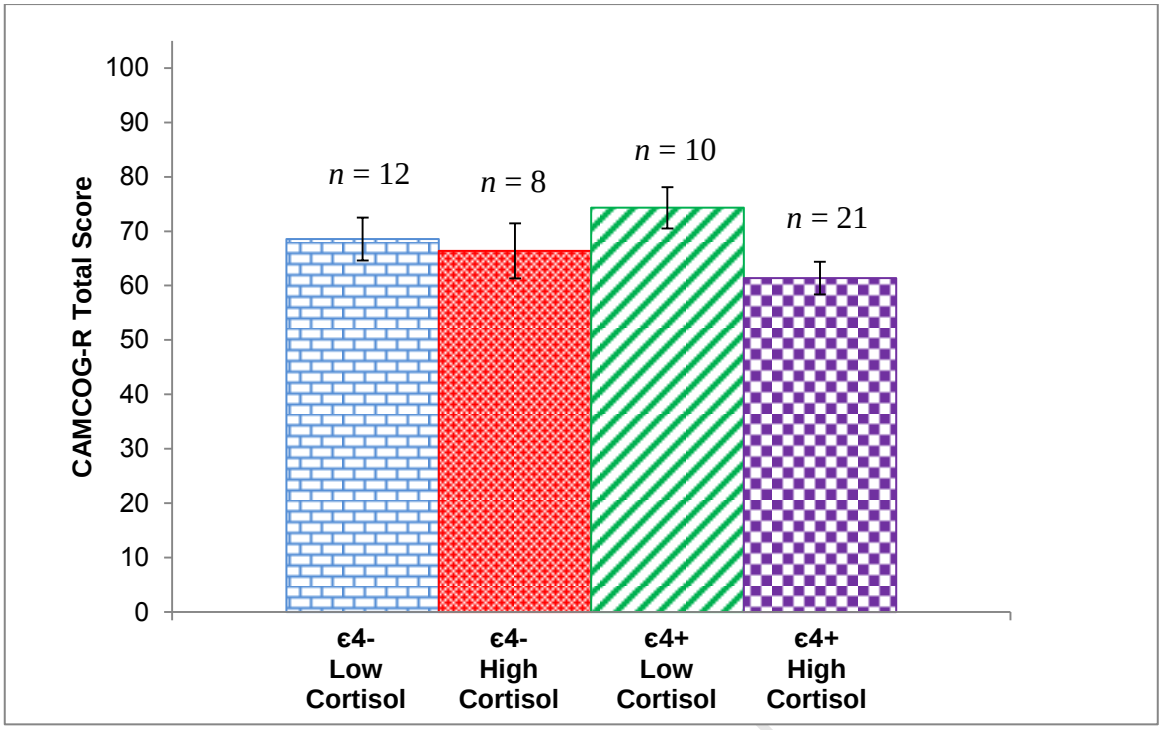


Figure 7. CAMCOG-R total scores in AD patients, grouped by cortisol levels and APOE-ϵ4 status. Cortisol: High or Low as defined by a median split. APOE-ϵ4 status: ϵ4+ = participants with the ϵ4 allele; ϵ4- = participants without the ϵ4 allele.

Exploratory analyses. In light of previously established links between cortisol and APOE-ϵ4 (Lee et al., 2008; Peavy et al., 2007), I wished to explore whether those participants who were ϵ4+ had higher levels of psychosocial stress and salivary cortisol than those who were ϵ4-. Exploring these data, I found that, among controls, those who were ϵ4+ had higher mean levels of psychosocial stress and cortisol than those who were ϵ4-, but these differences did not reach statistical significance (see Table 7). In the AD patient group, those who were ϵ4+ had higher means levels of psychosocial stress and cortisol than those who were ϵ4-; here, the differences for psychosocial stress also did not reach statistical significance, but those for cortisol were significant (see Table 8).

Table 7
Psychosocial Stress and Cortisol as a Function of Group and Apolipoprotein E Status in Controls (N = 65)

	Group				
	ϵ4+ (n = 24)	ϵ4- (n = 41)			
Variable	*M* (*SD*)	*M (SD)*	*t*	*p*	ESE
Psychosocial stress	19.13 (8.26)	16.90 (8.76)	1.01	.32	0.26
Cortisol	0.85 (0.25)	0.76 (0.33)	1.05	.30	0.31

Note. Values are means (and standard deviations). ϵ4+ = participants with the apolipoprotein ϵ4 allele; ϵ4- = participants without the apolipoprotein ϵ4 allele. Cortisol values are the log transformed cortisol value. ESE = effect size estimate, Cohen's *d*. For each between-group comparison, degrees of freedom = 63.

Table 8
Psychosocial Stress and Cortisol as a Function of Group and Apolipoprotein E Status in AD Patients (N = 64)

	Group				
	ϵ4+ (*n* = 37)	ϵ4- (*n* = 27)			
Variable	*M* (*SD*)	*M (SD)*	*t*	*p*	ESE
Psychosocial stress	22.30 (7.43)	20.33 (8.18)	1.00	.32	0.25
Cortisol	0.89 (0.34)	0.70 (0.28)	2.20	.03*	0.61

Note. Values are means (and standard deviations). ϵ4+ = participants with the apolipoprotein ϵ4 allele; ϵ4- = participants without the apolipoprotein ϵ4 allele. Cortisol values are the log transformed cortisol value. ESE = effect size estimate, Cohen's *d*. For each between-group comparison, degrees of freedom = 62.
*$p < .05$.

Hypotheses Set 4: Beta-Amyloid

To investigate the fourth set of hypotheses, the research team analysed levels of plasma Aβ in 10 controls and 30 AD patients. In 3 controls and 4 patients, the immunoassay kit could not detect levels of plasma Aβ. As this could have been due to a technical problem related to an interfering substance, I had to exclude these data from the analyses.

Table 9 presents demographic characteristics for the participants whose blood samples were analysed for levels of Aβ. Although group sample sizes were unequal, the data were normally distributed and the variances were similar; hence, I conducted *t*-tests to compare group levels of Aβ. These data indicate that the groups were similar in age, sex, and for cortisol levels, however, the AD patients had higher PSS scores.

Table 9
Demographic Data for Participants whose Aβ Samples were Analysed (N = 33)

	Group					
Variable	Controls (n = 7)	AD Patients (n = 26)	*df*	t / χ^2	*p*	ESE
Age	77.57 (4.65)	75.15 (5.45)	31	1.07[a]	.29	0.48
Sex (M:F)	2:5	9:17	1	.09[b]	.76	-0.05
PSS Score	14.71 (4.72)	22.15 (8.16)	31	-2.29[a]	.03*	1.12
Cortisol	0.83 (0.36)	0.93 (0.32)	28	-0.67[a]	.51	0.29

Note. For the variables *Age*, *PSS Score*, and *Cortisol*, means are presented with standard deviations in parentheses. PSS = Perceived Stress Scale – measure of psychosocial stress. Cortisol values are the log transformed values. [a]Test statistic for *t*-test. [b]Test statistic for χ^2. ESE = effect size estimate (in this case, Cohen's *d* for *t*-tests, and φ for χ^2).
*$p < .05$.

Although the data presented in Table 10 suggest that AD patients had a slightly lower Aβ1-42/Aβ1-40 ratio than controls, the between-group difference was not statistically significant, thus disconfirming *Hypothesis 4a*. AD patients had slightly lower levels of plasma Aβ1-42 and slightly higher levels of Aβ1-40 than age-matched controls.

Hypothesis 4b was not confirmed. The analyses showed that the plasma Aβ1-42/Aβ1-40 ratio (n = 14, M = .24, SD = .05) in AD patients with high psychosocial stress (as defined by a median split) was not lower than the ratio (n = 12, M = .21, SD = .06) in AD patients with low psychosocial stress, $t(24) = -1.30$, p = .21, d = 0.13. The

analyses also showed that the plasma Aβ1-42/Aβ1-40 ratio (n = 13, M = .22, SD = .06) in AD patients with high cortisol (as defined by a median split) was not lower than the ratio (n = 13, M = .23, SD = .05) in AD patients with low cortisol, $t(24) = -0.48$, $p = .64$, $d = 0.18$.

Table 10
Levels of Aβ *in Controls and AD Patients (N = 33)*

	Group					
	Controls	AD Patients				
Beta-amyloid	(n = 7)	(n = 26)	*df*	*t*	*p*	ESE
Aβ1-42	42.57 (22.47)	40.19 (13.23)	31	0.36	.72	0.13
Aβ1-40	165.29 (82.48)	181.81 (53.97)	31	-0.64	.53	0.24
Aβ1-42/Aβ1-40 Ratio	0.26 (0.02)	0.22 (0.05)	31	1.51	.14	1.05

Note. Values are means (and standard deviations). Aβ = beta-amyloid. ESE = effect size estimate (in this case, Cohen's *d*).

Exploratory analyses. A low plasma Aβ1-42/Aβ1-40 ratio has been associated with the development and progression of AD patients over a period of 18 months (Koyama et al., 2012; Rembach et al., 2013). To explore this I chose to examine the relationship between the plasma Aβ1-42/Aβ1-40 ratio and cognitive scores across the entire sample. Figure 8 demonstrates a positive and significant relationship between the plasma Aβ1-42/Aβ1-40 ratio and cognitive scores as measured by the CAMCOG-R total score, $r(31) = .63$, $p < .001$. When analysed separately in each group, there was no relationship in the controls, $r(5) = .08$, $p < .87$. In the AD patient group there was a significant positive relationship, $r(24) = .64$, $p < .001$

Elevated levels of glucocorticoids have been associated with increased Aβ formation and deposition in animal models (Dong & Csernansky, 2009; Green, et al., 2006; Kulstad et al., 2005) and in humans (Toledo et al., 2012). Similarly, in rats, psychosocial stress has been found to exacerbate Aβ-induced short-term memory deficits (Srivareerat, Tran, Alzoubi, & Alkadhi, 2009), and to intensify levels of beta-site APP-cleaving enzyme (Alkadhi, Alzoubi, Srivareerat, & Tran, 2012). Based on these findings, I performed exploratory correlational analyses examining relationships between beta-amyloid, cortisol, and stress in the current sample. Across the entire sample, there were no significant correlations between Aβ1-42 and psychosocial stress (as measured by the PSS), $r(31) = .22$, $p = .23$, or between Aβ1-42 and morning cortisol levels, $r(31) = -14$, $p = .44$. Similarly, there were no significant correlations between

Aβ1-40 and psychosocial stress, $r(31) = .10$, $p = .58$, or between Aβ1-40 and cortisol, $r(31) = .08$, $p = .66$, or between psychosocial stress and the Aβ1-42/Aβ1-40 ratio, $r(31) = .23$, $p = .21$. There was, however, a significantly negative relationship between cortisol and the Aβ1-42/Aβ1-40 ratio, $r(31) = -0.37$, $p = .03$.

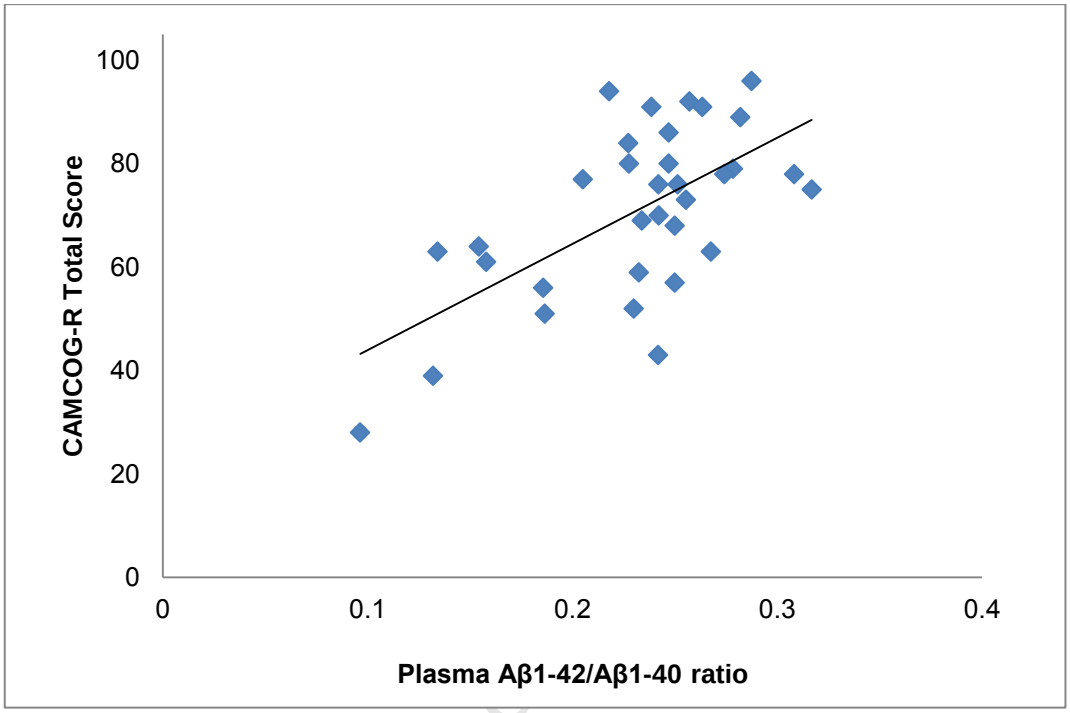


Figure 8. The relationship between the plasma Aβ1-42/Aβ1-40 ratio and cognitive scores as measured by the CAMCOG-R total score across the sample (*N* = 33).

Hypotheses Set 5: Hippocampal Volume

This set of hypotheses relates to hippocampal volumes, as determined from the structural MRI scans. Five of the selected participants for the MRI scan did not complete the scan (4 patients and 1 control; these participants were all females and were aged 67, 83, 70, 79, and 74 respectively), and so the final sample size for this component of the study was *N* = 35 (Controls *n* = 14, AD patients *n* = 21).

Hypotheses 5a and *5b* related to hippocampal volume, stating that (*5a*) AD patients will have smaller ICV-adjusted hippocampal volumes than controls, and that (*5b*) AD patients with higher baseline cortisol levels and the APOE-ϵ4 allele will have smaller ICV-adjusted total hippocampal volumes than patients with low baseline cortisol levels and no ϵ4. Table 11 presents demographic data for the subset of participants who had MRI scans and for whom hippocampal volumes were recorded.

The control and AD patient groups were well matched for age, sex, and handedness. AD patients tended to have higher PSS scores than controls but the cortisol levels between the groups were similar. AD patients had significantly fewer years of education and performed significantly worse on the MMSE and Learning subscale.

Before testing *Hypotheses 5a* and *5b*, I adjusted the absolute hippocampal volumes for total ICV by dividing hippocampal volume by total ICV for each participant. Overall, male participants (n = 15, M = 1.52E-6, SD = 1.89E-5) had larger ICVs (mm^3) than female participants (n = 20, M = 1.25E-6, SD = 1.27E-5), $t(33)$ = 5.00, $p < .001$, d = 0.17. There were no significant associations between ICV and age, or between ICV and cognitive functioning (as measured by MMSE score).

Table 11
Demographic Data for Participants with MRI Scans (N = 35)

	Group					
Variable	Controls (n = 14)	AD Patients (n = 21)	df	t / χ^2	p	ESE
Age	72.43 (6.24)	75.57 (7.86)	33	-1.25[a]	.22	0.44
Sex (M:F)	5:9	10:11	1	0.49[b]	.49	-0.12
Education (years)	13.29 (3.10)	10.00 (2.74)	33	3.30[a]	.002**	1.12
Handedness (R:L)	13:1	18:3	1	0.42[b]	.52	-0.11
PSS score	16.43 (5.02)	20.62 (6.75)	33	-1.98[a]	.06	0.70
Cortisol	6.19 (4.28)	5.29 (4.42)	33	0.61[a]	.55	0.21
MMSE	28.57 (1.22)	20.00 (4.62)	33	6.76[a]	< .001***	2.54
Learning Score	14.93 (1.27)	6.52 (3.92)	33	7.72[a]	< .001***	2.88

Note. For the variables *Age*, *Education*, *PSS Score*, *Cortisol*, *MMSE*, and *Learning Score*, means are presented with standard deviations in parentheses. PSS = Perceived Stress Scale. MMSE = Mini-Mental State Examination. [a]Test statistic for t-test. [b]Test statistic for χ^2. ESE = effect size estimate (in this case, Cohen's d for t-tests and φ for χ^2 tests).
**$p < .01$. ***$p < .001$.

Table 12 presents the relationships between key demographic variables and ICV-adjusted hippocampal volumes in controls and AD patients. In controls, age was negatively correlated with right, left, and total hippocampal volumes, and sex was positively correlated with left and total hippocampal volume. In AD patients, there were no significant associations with age or sex. There were significant associations in this group between education and right, left, and total hippocampal volumes. In both the

controls and AD patients, there were no associations between ICV-hippocampal volumes and MMSE or Learning subscale scores.

Correlations performed across the entire sample between ICV-adjusted hippocampal volumes (right, left, and total) and cognitive performance (as measured by the MMSE) showed significant associations: right HV, r(33) = .40, p = .02; left HV, r(33) = .37, p = .03; total HV, r(33) = .39, p = .02. Correlations performed across the entire sample between adjusted hippocampal volumes (right, left, and total) and Learning subscale score performance showed significant associations: right HV, r(33) = .48, p < .001; left HV, r(33) = .54, p < .001; total HV, r(33) = .57, p < .001.

Table 12
Correlations: Sociodemographic variables and ICV-adjusted hippocampal volume (N = 35)

	Group					
	Controls (n = 14)			AD Patients (n = 21)		
Variable	Left HV	Right HV	Total HV	Left HV	Right HV	Total HV
Age	-.67**	-.63*	-.65*	.07	-.01	.03
Sex	.60*	.53	.57*	-.02	.03	.01
Education	-.17	-.16	-.17	-.50*	-.49*	-.50*
MMSE	-.15	.08	-.12	.03	.11	.07
Learning	.41	.40	.41	.22	.33	.28

Note. HV = hippocampal volume. MMSE = Mini-Mental State Examination. Learning = Learning subscale score. For most correlations, the test statistic was Pearson's *r* correlation coefficient. For the categorical variable *Sex*, I used the point-biserial correlation coefficient.
*$p < .05$. **$p < .01$.

Confirming *Hypothesis 5a*, analysis of the absolute (unadjusted) and ICV-adjusted hippocampal volumes (see Table 13) indicated that AD patients had statistically significantly smaller hippocampal volumes than controls. This finding was true for right, left, and total hippocampal volumes.

Table 13
Between-Group Comparisons: Absolute and ICV-adjusted hippocampal volume (N = 35)

	Group				
	Controls (n = 14)	AD Patients (n = 21)			
Hippocampal volume	*M* (*SD*)	*M* (*SD*)	*t*	*p*	ESE
Absolute					
Left	1574.68 (231.99)	1055.74 (341.25)	4.96	< .001***	1.78
Right	1627.623 (229.82)	1151.85 (308.56)	4.92	< .001***	1.75
Total	3202.30 (442.28)	2207.59 (639.27)	5.06	< .001***	1.81
Adjusted					
Left	1.19E-3 (3.09E-4)	7.90E-4 (2.97E-4)	3.85	< .001***	1.39
Right	1.23E-3 (2.99E-4)	8.60E-4 (2.84E-4)	3.65	< .001***	1.26
Total	2.42E-3 (6.02E-4)	1.650E-3 (5.74E-3)	3.80	< .001***	1.30

Note. Absolute hippocampal volumes are presented in cubic millimetres. The ICV-adjusted hippocampal volumes are presented in scientific notation. ESE = effect size estimate (in this case, Cohen's *d*). For each between-group comparison, degrees of freedom = 33.
***$p < .001$.

Hypothesis 5b was not confirmed. A univariate ANOVA detected no significant main effect of cortisol, $F(3, 12) = 0.18$, $p = .68$, $\eta_p^2 = .02$, and no significant cortisol x APOE-ϵ4 interaction effect, $F(3, 12) = 2.73$, $p = .12$, $\eta_p^2 = .19$ on hippocampal volumes (see Figure 9). The analysis did, however, detect a significant main effect of APOE-ϵ4, where AD patients with APOE-ϵ4 had smaller ICV-adjusted total hippocampal volumes ($n = 10$, $M = 1.32E-3$, $SD = 2.01E-4$) than AD patients without APOE-ϵ4 ($n = 9$, $M = 1.95E-3$, $SD = 6.43E-4$), $F(3, 12) = 5.14$, $p = .04$, $d = 0.30$.

Exploratory analyses. Previous studies have indicated associations between cortisol and hippocampal volumes (Lupien et al., 1998; Tessner, Walker, Dhruv, Hochman, & Hamann, 2007), and between psychosocial stress and hippocampal volumes (Childress et al., 2013; Szeszko et al., 2006). In my study, across the entire sample, Pearson product-moment correlations between adjusted hippocampal volumes (right, left, and total) and cortisol levels, controlling for age and sex, showed no associations: right HV, $r(31) = .09$, $p = .63$; left HV, $r(31) = .04$, $p = .81$; total HV, $r(31) = .07$, $p = .72$. Across the entire sample, Pearson product-moment correlations between adjusted hippocampal volumes (right, left, and total) and psychosocial stress (as measured by the PSS), controlling for age and sex, showed no associations: right HV, $r(33) = -.07$, $p = .67$; left HV, $r(33) = -.09$, $p = .60$; total HV, $r(33) = -.08$, $p = .63$.

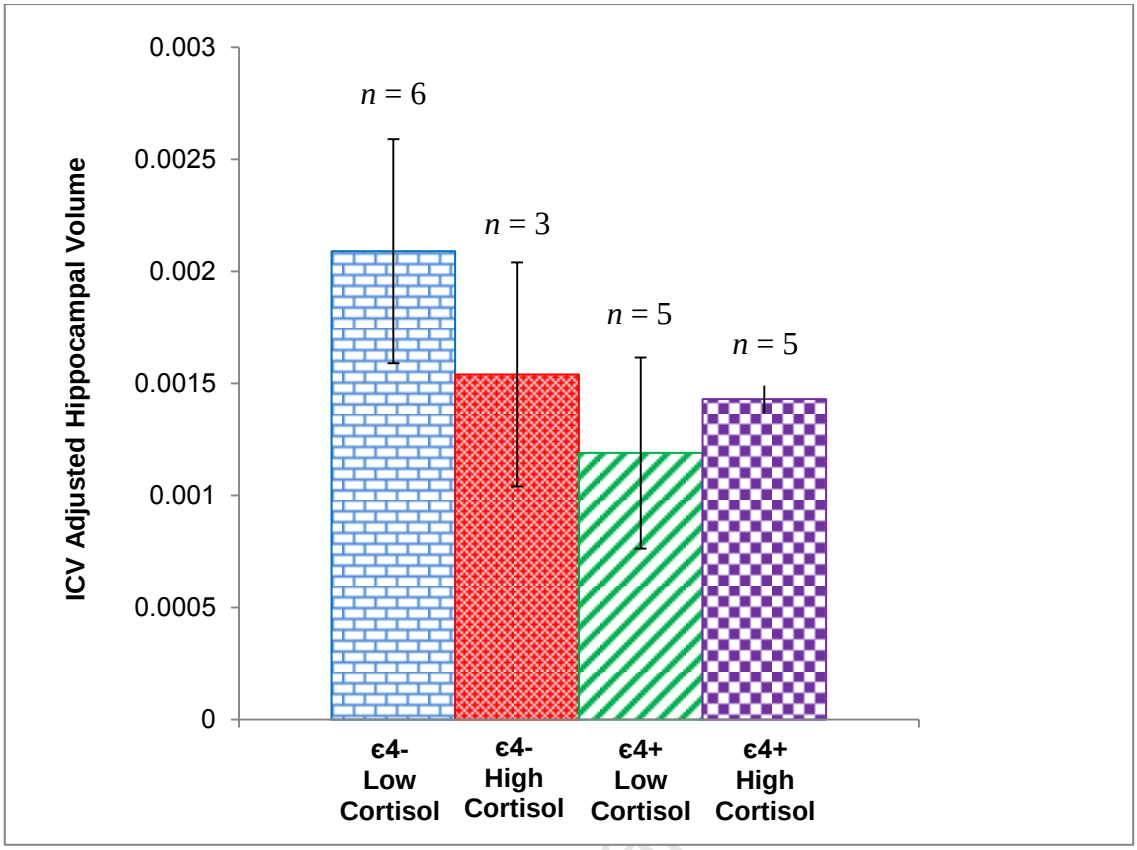


Figure 9. Intracranial volume-adjusted total hippocampal volumes (mm^3) in AD patients, grouped by cortisol levels and APOE-ϵ4 status. Cortisol: High or Low as defined by a median split. APOE-ϵ4 status: ϵ4+ = participants with the ϵ4 allele; ϵ4- = participants without the ϵ4 allele.

Multiple Regression Modelling

Given that a structural equation model could not be created based on the current data (see Appendix F), I performed hierarchical multiple regression modelling to examine which of the factors investigated above were significant predictors of cognitive functioning, as measured by CAMCOG-R Total Score. I entered the following predictors into the model, singly and separately and in this order: age (in years), sex (as a dichotomous variable: male:female), years of completed education, APOE-ϵ4 (as a dichotomous variable, i.e., allele present or absent), morning cortisol levels (log transformed), and psychosocial stress (as measured by the PSS).

Table 14 presents the results for each stage of the modelling process. Age, education, and APOE-ϵ4 were significant predictors; overall, the final model accounted for 42% of variance in the outcome. Cortisol and psychosocial stress accounted for very little variance in the model and were not significant predictors of the outcome.

Table 14

Hierarchical Multiple Regression Modelling of CAMCOG-R Total Score (N = 115)

Predictors	*B*	*SE B*	*β*
Step 1			
(Constant)	130.41	12.91	
Age	-0.68	0.18	-.34***
Step 2			
(Constant)	130.85	13.40	
Age	-0.68	.18	-.34***
Sex	-0.42	3.21	-.01
Step 3			
(Constant)	88.03	13.14	
Age	-0.41	0.16	-.21*
Sex	0.99	2.70	.03
Education	1.85	0.28	.52***
Step 4			
(Constant)	94.70	12.96	
Age	-0.44	0.15	-.22**
Sex	0.69	2.66	.02
Education	1.79	0.27	.50***
APOE-ϵ4	-6.83	2.43	-.21**
Step 5			
(Constant)	97.51	13.28	
Age	-.44	0.15	-.22**
Sex	0.63	2.66	.02
Education	1.80	0.28	.50***
APOE-ϵ4	-6.32	2.48	-.19*
Cortisol	-3.83	3.93	-.07
Step 6			
(Constant)	108.01	15.37	
Age	-0.51	0.16	-.26**
Sex	0.38	2.66	.01
Education	1.70	0.28	.47***
APOE-ϵ4	-5.70	2.52	-.17**
Cortisol	-4.33	3.94	-.08
PSS	-0.21	0.16	-.11

Note. CAMCOG-R = Cambridge Cognitive Examination-Revised. The predictor variable *Education* refers to number of years of completed education. The predictor variable *APOE-ϵ4* refers to apolipoprotein ϵ4. The predictor variable *Cortisol* refers to the log transformed values of the salivary cortisol measure. The predictor variable *PSS* refers to the Perceived Stress Scale – measure of psychosocial stress. *B* = unstandardized coefficients for beta. *SE B* = standard error of *B.*

β = standardized coefficients for beta. R^2 = multiple regression correlation coefficient. ΔR^2 = change in multiple regression correlation coefficient.

For Step 1: $R^2 = .12$, $\Delta R^2 = .12$; Step 2: $R^2 = .12$, $\Delta R^2 < .001$;

Step 3: $R^2 = .36$, $\Delta R^2 = .25$; Step 4: $R^2 = .41$, $\Delta R^2 = .04$; Step 5: $R^2 = .41$, $\Delta R^2 = .01$;

Step 6: $R^2 = .42$, $\Delta R^2 = .01$.

*$p < .05$**$p < .01$. ***$p < .001$.

I performed diagnostic tests on the model; Table 15 provides details of these. Briefly, analysis of the partial correlations confirmed that age, education, and APOE-ϵ4 contributed to the majority of the variance in the model. Psychosocial stress and cortisol did not predict much unique variance. The tolerance levels were high, suggesting that there were no problems with multicollinearity. Values for the Durbin-Watson statistic (1.29) and Variance Inflation Factor (< 1.09) also confirmed that there were no problems with multicollinearity. Examination of the residuals indicated that there were four potential outliers. I then excluded these four participants and performed the regression model again. Excluding these participants did not change the results of the initial model and thus these participants were retained in the regression model reported in Table 14.

Table 15
Hierarchical Multiple Regression Model: Diagnostic data

Predictor	Partial correlation	Semi-partial correlation	Tolerance
Age	-.34	-.34	1.00
Education	-.26	-.21	0.99
APOE-ϵ4	.53	.50	0.93
Cortisol	-.09	-.07	0.95
PSS	-.13	-.10	0.83

Note. The predictor variable *Education* refers to number of years of completed education. The predictor variable *APOE-ϵ4* refers to apolipoprotein ϵ4. The predictor variable *PSS* refers to the Perceived Stress Scale – measure of psychosocial stress.

Summary of Results

This cross-sectional study investigated the relationships between sociodemographic variables, psychosocial stress, cortisol, APOE-ϵ4, Aβ, and hippocampal volume in a sample of South African older adults with and without cognitive impairment. The most significant finding emerged from the multiple regression analysis that explored several of the abovementioned variables in relation to cognitive functioning. Because this was the most comprehensive model to be explored in this study, I will summarize these findings first. Then, I will then summarize the results pertaining to the relationships between stress, psychological and physiological, and APOE-ϵ4, Aβ, and hippocampal volume. The purpose of that section, then, will be to summarize the results pertaining to the relationships between stress and the other factors of interest. In-depth interpretation and discussion of the results from this study (as well as those from Study 2) appear in the *General Discussion*.

Integrated Model of Factors Associated with Cognitive Functioning

The appearance, and acceleration, of cognitive decline in older adults has been the focus of much research over the past several decades. This research has identified several putative risk factors for age-related cognitive impairment (and for the development of AD). Several of these factors are also related to the experience of stress, and its neurobiological and cognitive consequences. A major aim of this research was to examine the roles of these common factors in cognitive functioning across a spectrum of healthy to impaired cognition in AD, as well as their associations with stress in older adults. Regarding sociodemographic characteristics of the study sample, on average controls were significantly younger than AD patients and had more years of education. Although most participants in both groups were female, the sex distribution across groups was not statistically significantly different. AD patients did, however, have significantly lower SES status than controls; most AD patients had a monthly household income of less than ZAR2500.

Because the groups differed significantly on some sociodemographic variables, these variables (*viz*., age and education) were entered first into the regression model. This strategy allowed examination of the effects on cognitive functioning of other variables of interest (psychosocial stress, cortisol, and APOE-ϵ4) over and above the potentially confounding variables of age and education. Although there was no

significant between-group difference in sex distribution, I included the variable in the model because (a) there were more females than males in the sample, and (b) female sex has been associated with increased risk for AD (Holland, Desikan, Dale, & McEvoy, 2013; Vina & Lloret, 2010).

Although there were significant between-group differences in terms of both SES status and level of education, only the latter featured as a predictor in the regression model. In this way, I sought to limit redundancy, and possible multicollinearity, because of the strong positive association between education and SES status, $r(128) = .57$, $p < .001$. Even in South Africa, where race and SES status were so closely entwined for so many years, educational attainment is (as in other countries) a key marker of SES status in terms of its influence on job opportunities and earning potential (Adler & Newman, 2002; Miech & Hauser, 2001).

In summary, I entered the following predictor variables, in this order, in the hierarchical regression model: age (in years), sex (male or female), education (in years), APOE-ϵ4 (as a dichotomous variable, i.e. allele present or absent), morning cortisol levels (log transformed values), and self-perceived psychosocial stress (as measured by the PSS). The outcome variable was cognitive functioning, as measured by CAMCOG-R Total score. In the final model, age, education, and APOE-ϵ4 were the only significant predictors of cognitive functioning in the current sample; that model accounted for 42% of the variance in the outcome variable.

Based on previous findings reported in the literature, I performed a number of analyses to examine the relationships between cognitive functioning, resilience, APOE-ϵ4, Aβ, and hippocampal volumes, on the one hand, and psychosocial and physiological stress, on the other. This section will provide a summary of those findings which are summarized in order of the hypothesis-driven analyses and then the exploratory analyses; the *General Discussion* chapter offers further interpretation and discussion of these findings.

Hypothesis-Driven Analyses

Hypotheses Set 1. *Hypothesis 1a* was partially confirmed: Compared with controls, AD patients had higher levels of psychosocial stress, but they did not have more lifetime experiences of traumatic life events or higher cortisol levels. *Hypothesis 1b* was not confirmed: AD patients did not demonstrate a larger positive association

between psychosocial stress and cortisol levels than controls. *Hypothesis 1c* was not confirmed: levels of psychosocial stress and cortisol were not negatively correlated with cognitive performance when examined separately in each group, or when examined across the entire sample in the regression model.

Hypotheses Set 2. *Hypothesis* 2a was confirmed: In controls, AD patients, and across the entire sample, there was a significant negative correlation between levels of resilience and psychosocial stress. *Hypothesis 2b* was not confirmed: No association was found between resilience and education in either group or across the entire sample.

Hypotheses Set 3. *Hypothesis 3a* was confirmed: AD patients had a higher APOE-ϵ4 allelic frequency than controls. *Hypothesis 3b* was not confirmed: AD patients who were ϵ4 carriers did not perform more poorly on a measure of cognition than non-carriers. *Hypothesis 3c* was not confirmed: AD patients with high levels of cortisol and the presence of the ϵ4 allele did not perform more poorly on a measure of cognition than those AD patients with low levels of cortisol and an absence of the ϵ4 allele.

Hypotheses Set 4. *Hypothesis 4a* was not confirmed: AD patients did not have a significantly lower plasma Aβ1-42/Aβ1-40 ratio than controls. *Hypothesis 4b* was not confirmed: AD patients with high levels of psychosocial stress and cortisol did not have a lower plasma Aβ1-42/Aβ1-40 ratio than AD patients with low levels of psychosocial stress and cortisol.

Hypotheses Set 5. *Hypothesis 5a* was confirmed: AD patients had smaller ICV-adjusted hippocampal volumes than controls. *Hypothesis 5b* was not confirmed: AD patients with high cortisol levels and APOE-ϵ4 did not have smaller ICV-adjusted hippocampal volumes than AD patients with low cortisol levels and without APOE-ϵ4.

Exploratory Analyses

Exploratory analyses were performed for several variables based on previous findings in the literature. Below, I discuss the results from the exploratory analyses in the order in which they were performed, namely, for psychosocial stress, cortisol, APOE-ϵ4, Aβ, and hippocampal volumes.

Exploratory analyses were performed for the measures of psychosocial and physiological stress in relation to demographic variables. Psychosocial stress was found to decrease with age in both groups. In controls, females had significantly higher levels

of psychosocial stress than males. In AD patients, males were found to have significantly higher levels of psychosocial stress than females. There were no sex differences for lifetime experiences of stress. There were no significant between-group differences in terms of mean morning salivary cortisol levels. There were also no age- or sex-related effects for cortisol.

Exploratory analyses for APOE-ϵ4, in both control and AD patient groups, did not find that participants who were APOE-ϵ4 carriers had higher levels of psychosocial stress. In controls, APOE-ϵ4 carriers also did not have higher levels of salivary cortisol than those who were not carriers; however in the AD patient group APOE-ϵ4 carriers had higher salivary cortisol level than those who were not carriers. Investigating the combination of psychosocial stress and APOE-ϵ4 on cognitive performance (as measured by CAMCOG-R Total score), there was no significant main effect of either psychosocial stress or APOE-ϵ4 carrier status on cognitive function; there was also no significant interaction effect.

Exploratory analyses performed for the plasma Aβ1-42 or Aβ1-40 concentrations across the entire sample found no significant correlations between Aβ1-42 or Aβ1-40 and psychosocial stress. There were no significant correlations between Aβ1-42 or Aβ1-40 and cortisol.

Exploratory analyses for hippocampal volume and stress, indicated that across the entire sample there were no significant correlations between ICV-adjusted hippocampal volumes (right, left, or total) and psychosocial stress or cortisol.

In summary, the regression analyses demonstrated that age, level of education, and APOE-ϵ4 carrier status were significant predictors of cognitive function in this sample of South African older adults. Psychosocial and physiological stress was largely unrelated to cognitive function and to the other variables in this study. In general, my hypotheses for this cross-sectional study were not confirmed. The hypotheses that were confirmed related to APOE-ϵ4 and hippocampal volume.

CHAPTER THREE: STUDY 2 – A LONGITUDINAL STUDY

Introduction

Longitudinal Studies of AD

Although there is a wealth of cross-sectional research on AD, there is a comparative paucity of longitudinal studies. Cross-sectional studies have their advantages, in that they can examine various outcome variables at one time point (Mann, 2003). Also, cross-sectional studies allow for a single point estimate to be used as the dependent measure; in the context of predictable variables, this can be useful for estimating the likelihood of future disease course and progression (Fotenos, Snyder, Girton, Morris, & Buckner, 2005). Although cross-sectional research design has the benefit of measuring several variables at once, it cannot provide distinct information pertaining to cause-and-effect relationships. Furthermore, it is likely that differences found in cross-sectional research represent entrenched differences that were established prior to old age; these factors may, therefore, not be the same as those that influence decline (Alley et al., 2007). Longitudinal research allows for the observations of developments over time at an individual and group level. Furthermore, it has the capacity for establishing sequences of events, and thus causal relationships, provided the study is started prior to the onset of disease. Repeated measurement of cognitive decline at several time points provides a more reliable estimation of long-term cognitive change. Based on the progressive cognitive decline that is a defining feature of AD, the ability to monitor such cognitive change over time and to assess the contribution of different factors to this change confirms the utility and relevance of longitudinal research of AD.

The history of AD research is dominated by cross-sectional studies. This is surprising given that declining cognition over time is the principal clinical manifestation of AD. There is evidence for a preclinical period in which the pathophysiological process of AD in the brain may have commenced, but in which the clinical symptoms of AD such as cognitive impairment are too mild to be detected (Morris & Price, 2001; Price et al., 2009). These undetected changes pose problems for investigating possible preceding risk factors for AD and the causal role of such factors in cognitive impairment. Longitudinal studies, especially in the case of AD given the

progressive nature of the disease, are therefore useful because they can track changes over time and allow for the predictive value of certain factors to be explored. While some factors have been identified as risk factors for developing the disease, it is less clear what influence these factors have in the course of neurodegeneration as the disease progresses.

Cognitive decline represents a continuum of cognitive changes from normal ageing, to MCI, to dementia (Plassman, Williams, Burke, Holsinger, & Benjamin, 2010). Therefore it makes sense to perform longitudinal studies that include a range of adults along this continuum. Longitudinal studies that include older adults who are cognitively healthy at baseline are particularly useful for detecting cognitive changes that may not have warranted a clinical diagnosis of cognitive impairment at cross-sectional assessment (Johnson, Storandt, Morris, & Galvin, 2009). Early identification of cognitive changes over time might denote that a process of cognitive decline has commenced and may be an indicator of Alzheimer's disease in its early stages. For example, Sliwinski, Lipton, Buschke, and Stewart (1996) reported that mild AD may be present in some older people who appear clinically 'normal', and that memory loss may be apparent approximately 5-7 years prior to the clinical diagnosis of dementia. This report suggests that estimates of cognitive change in healthy samples may be negatively biased in cross-sectional studies; one of the limitations of cross-sectional studies of AD is that they can only provide a snapshot of cognitive functioning.

Cognitive decline in ageing is not restricted to one domain of cognition, such as memory; other cognitive domains are often involved and should also be explored in relation to cognitive decline (Park & Reuter-Lorenz, 2009; Wilson et al., 2002). For instance, evidence of multi-domain cognitive decline is provided by Cullum et al. (2000) who investigated the change in several different domains of cognition (as measured by MMSE total score, CAMCOG total score, and individual scores on eight CAMCOG subscales) over 4 years in a sample of non-demented older adults. They reported an annual rate of change of -1.6 points on the CAMCOG total score, and found statistically significant decline on several CAMCOG subscale scores. Similarly, Johnson et al. (2009) performed a longitudinal study to model cognitive decline in preclinical AD. Results showed accelerating cognitive decline, not just in memory, but in multiple domains. Assessment of memory alone may not be sufficient for the detection of cognitive impairment if the memory deficits are mild. The above findings reported by Johnson et al., indicate the relevance of assessing cognition across several

domains, as mild changes across other domains will also indicate incipient cognitive impairment. Studies such as these confirm the presence across time of cognitive changes in multiple domains in older adults.

Of the longitudinal studies performed in ageing, one particularly notable example of successful longitudinal research in older adults is The Nun Study (e.g. Butler & Snowdon, 1996; Mortimer, 2012; Greiner, Snowdon, & Greiner, 1996). This project is a collaborative effort between the University of Minnesota and the School Sisters of Notre Dame congregation. Its participants are 678 American members of the School Sisters of Notre Dame religious congregation who are between the ages of 75 and 106 years, representing a broad distribution of function and health. In one of the studies that examined data from within this large project, Butler, Ashford, and Snowdon (1996) investigated age, education, and change in MMSE scores in a population sample of older nuns. Their results indicated that cognitive function as measured by the MMSE decreased over an average of 1.6 years within individuals, and the extent of the decline increased with age in those sisters who held a bachelor's degree. These data raise the question about the role that demographic factors, such as education, may play in cognitive decline in the elderly.

Another prospective longitudinal study of the antecedents of ageing is the Baltimore Longitudinal Study of Aging (Kawas, Gray, Brookmeyer, Fozard, & Zonderman, 2000). One set of findings from this study demonstrated age-specific incidence rates of AD and showed a trend for increased incidence in women and in individuals with fewer years of education.

Longitudinal studies of cognitive change have also been performed in individuals who are already cognitively impaired. For example, Suh, Ju, Yeon, and Shah (2004) investigated rates of cognitive decline in a 1-year longitudinal observational study of AD patients. The sample consisted of 107 AD patients who were assessed at three time points, namely, at 0, 6, and 12 months. Using mixed-model analyses, Suh et al. found that the average annual rate of cognitive decline in AD patients was 2.3 MMSE points.

Unfortunately, many studies investigating cognitive decline using longitudinal designs have been fraught with methodological problems. One such problem is the use of a single measurement follow-up (i.e. two observations in total). If only a single measurement follow up is used, it is difficult to reliably discern chance variability from person-specific patterns of change (Wilson et al., 2002).

In addition to the methodological problems that afflict its investigation, cognitive decline is difficult to pin down because (a) it is not linear, and (b) it is affected by numerous factors that can vary in, and between, individuals (Daviglus et al., 2010).

What is evident, though, is that cognitive decline is worse in those individuals who are already cognitively impaired at baseline measurement than in those who are cognitively healthy at that time (Butler, Ashford, & Snowdon, 1996). Although it is not entirely clear which factors contribute to the speed of cognitive decline, different factors may vary in their effect on cognitive change among people with healthy cognition and those with pre-existing cognitive impairment. There is evidence for the wide variability, on an individual level, in age-related cognitive decline pertaining to initial level of cognitive function and rate of decline (Wilson, Beckett, Bennett, Albert, & Evans, 1999). AD, a clinically heterogeneous disease characterized by progressive incapacitating cognitive impairment, is prone to such individual variability in its course and progression. Wilkosz et al. (2010) explored this variability by identifying trajectories of cognitive decline in AD. Their results showed that six trajectories represented patterns of change in MMSE score, with significantly different courses and rates of cognitive decline for the majority of the AD participants. These trajectories included initial MMSE, age, gender, education, APOE-ϵ4, and psychosis. The trajectories were best defined by the participants' initial MMSE score and age; older participants with higher initial MMSE score tended to follow trajectories of slower cognitive decline. In light of the variability found in cognitive decline, the following section discusses the role of various factors that might affect rate of cognitive decline in both healthy older adults and AD patients.

Factors Associated with Cognitive Change and Decline in Older Adults

A recent systematic review suggests there is insufficient evidence to support an association between cognitive decline and many of its proposed risk factors, i.e., risk factors for cognitive decline in the first case (Plassman et al., 2010). Their review summarizes evidence about putative risk and protective factors for cognitive decline in older adults. The factors that were considered included nutritional factors, medical factors and medications, social, economic, behavioural factors, toxic environmental exposure, and genetic factors. They reported that only a handful of the factors showed

adequate evidence to favour an association with cognitive decline; these factors were current tobacco use, the APOE-ϵ4 genotype, and certain medical co-morbidities such as diabetes mellitus and the metabolic syndrome. Stern et al. (1994) investigated the annual rate of cognitive change in patients with AD over a period of up to 90 months; they also explored the effects of dementia severity, gender, age at onset, family history of dementia, and prior rate of cognitive decline, on that rate. They found that none of these variables predicted the rate of cognitive deterioration, other than the degree of cognitive impairment and previous rate of decline based on scores from the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog). Similarly, Suh et al. (2004) found, in a longitudinal study using a sample of AD patients, that cognitive decline was not predicted by years of education or duration of AD since onset.

Recent observational studies, though, have identified several factors associated with increased rate of cognitive decline. These factors included higher age and lower initial MMSE score (Wilkosz et al., 2010); presence of Type 2 diabetes, higher systolic blood pressure, higher serum triglycerides (Umegaki et al., 2012); smoking (Peters et al., 2008); and elevated cardiovascular risk (Dregan, Stewart, & Gulliford, 2013). Likewise, some studies have identified factors that may protect against cognitive decline. These protective factors included statin use (Szwast et al., 2007); physical fitness (Sattler, Erickson, Toro, & Schroder, 2011); and cognitive reserve (Tucker & Stern, 2011).

It is beyond the scope and purpose of this dissertation to review all of the above-mentioned factors in detail. Rather, the following sections of this literature review will focus on some specific factors that have been associated with increased rate of cognitive decline. The reason for choosing these is that they are central to the main focus of this thesis, namely, psychosocial and physiological stress, and that some of them - age, education, and APOE-ϵ4 - were identified in Study 1 as being significant predictors of cognitive function in older adults across a spectrum of cognitive functioning. I shall review the literature in the order of physiological factors, psychosocial factors, and then sociodemographic factors.

Physiological factors. The physiological factors discussed below include changes in the hypothalamic-pituitary-adrenal axis and APOE-ϵ4.

Changes in the hypothalamic-pituitary-adrenal axis. Associations have been established between increases in HPA-axis activity and impairment in cognitive functioning (O'Brien, Ames, Schweitzer, Mastwyk, & Colman, 1996; Sandstrom et al.,

2011). The focus of these studies has been especially on the glucocorticoid, cortisol, which is a marker of physiological stress and HPA axis activity. The glucocorticoid cascade hypothesis of the pathophysiology of AD states that excessive quantities of circulating glucocorticoids can lead to neuronal cell death in the hippocampus (Backman et al., 2005; Sapolsky, Krey, & McEwen, 1986). This damage to the hippocampus may then result in further HPA-axis dysfunction. The latter, in turn, causes more hypercortisolism and this further contributes to hippocampal dysfunctioning (Weaver et al., 2004).

Swanwick et al. (1998) investigated HPA-axis dysfunction in AD in a cross-sectional and longitudinal study using the dexamethasone suppression test. This test measures the response of the adrenal glands to ACTH after the administration of dexamethasone, a synthetic version of cortisol (Miller, Chen, & Zhou, 2007). Participants included 30 patients with probable AD and 17 healthy older adults. The researchers measured participants' cortisol levels before and after administration of 1mg of dexamethasone. The dexamethasone administration and cortisol measurements were repeated at two 9-month follow-up periods. The results of the cross-sectional study were not consistent with the longitudinal study: HPA-axis dysfunction was associated with severity of dementia at baseline, but it did not persist at follow-up and cortisol levels did not increase over time. In summary, these data did not support the glucocorticoid-cascade hypothesis of AD progression.

In another longitudinal study of cortisol levels over time, Weiner, Vobach, Svetlik, and Risser (1997) determined plasma cortisol concentrations in 19 probable AD patients. Cortisol concentrations were measured at 12 noon and then several times between 13:00 and 16:00 hours for the Afternoon Cortisol Test, which established average 24 hour cortisol levels. These cortisol measurements were performed at the initial assessment and at 12 monthly intervals over a period of two to three years. They found that none of the cortisol measures increased over the study period, and the Afternoon Cortisol Test, used to estimate the average 24 hour cortisol reading, was not associated with more rapid cognitive decline. However, they did find that the baseline 12 noon cortisol measurement was associated with more rapid cognitive decline.

An association between cortisol and cognitive decline has been reported in other studies. For instance, Lupien et al. (1994) explored the relationship between basal cortisol levels and cognitive decline in a small sample (N = 19) of healthy older adults over a four-year period. These adults had previously been shown to differ in their

cortisol levels. The researchers found that the combination of increased plasma cortisol over time and a high final level of cortisol predicted worse memory performance over time. Csernansky and colleagues (2006) explored whether raised plasma cortisol levels were associated with clinical and cognitive measures of the rate of disease progression in participants with AD. Their study included 33 participants with very mild and mild AD and 21 cognitively normal participants; each had a cognitive assessment annually for up to 4 years. Results from growth curve models supported the researchers' hypothesis that elevated morning plasma glucocorticoid hormone levels were associated with the rate of change of both clinical and cognitive measures of dementia severity in participants with AD. The association between plasma cortisol and memory function was particularly prominent, as it lent support to the idea that elevated glucocorticoid levels affect progression of AD, especially with regard to the amnesia associated with hippocampal degeneration (Serrano-Pozo et al., 2011).

Clearly, the findings reported by Lupien et al. (1994), Weiner et al. (1997), and Csernansky et al. (2006) stand in contrast to those reported by Swanwick and colleagues (Swanwick et al., 1998; Weiner, Vobach, Svetlik, & Risser, 1993). A possible explanation for this difference relates to the different stages of AD. Swanwick et al. (1998) included a mixture of very mild, mild, and moderate probable AD patients, while the other studies included either cognitively healthy controls (Lupien et al., 1994) or very mild and mild AD patients (Csernansky et al., 2006; Weiner et al., 1997). There is evidence that the rate of cognitive decline may vary at different points during the disease (Stern et al., 1994). Furthermore, Bunce et al. (Bunce, Fratiglioni, Small, Winblad, & Backman, 2004) found that cognitive decline was most prominent approximately 3 years prior to a clinical diagnosis of AD, with an abrupt decline shortly before diagnosis. Thus the mixture of AD patients in Swanwick's study, particularly the inclusion of patients with mild and moderate AD, may have diluted the effects of cortisol on cognition. Swanwick and colleagues acknowledge that the glucocorticoid hypothesis may only be relevant in the early stages of AD. In support of this, Csernansky and colleagues (2006) reported significant correlations between plasma cortisol concentrations and measures of disease progression in participants with very mild dementia but not in those with mild dementia.

Drawing on the combined evidence from the studies discussed above, it is clear that there is marked variability in the effects of cortisol on cognitive decline. What

seems to be evident, however, is that the stage and severity of AD should be taken into account when exploring the association between cortisol and cognitive decline.

Apolipopoprotein є4. Individuals who carry the APOE-є4 allele have an increased risk of developing AD. The evidence suggests that APOE-є4 may play a role prior to the clinical (symptomatic) phase of the disease. However, once clinical disease is established, the contribution of APOE-є4 to cognitive decline within the disease remains unclear.

The majority of studies investigating APOE-є4 and cognition have included population samples that were followed up over several years, thus providing data for cognitively healthy participants, incident AD, and AD progression. One such study investigated the association between APOE-є4 and rate of cognitive decline in community-dwelling older adults with and without dementia (Jonker, Schmand, Lindeboom, Havekes, & Launer, 1998). Included in this 4-year longitudinal study were participants identified at baseline as having normal cognition, minimal dementia, or dementia. The presence of the APOE-є4 allele was found to be significantly associated with cognitive decline in those participants who were cognitively normal at baseline, but was not associated with decline in participants with mild dementia and dementia. More recently, however, Schiepers et al. (2012) found that in cognitively healthy older adults, the presence of APOE-є4 predicted more accelerated cognitive decline over 8 years (between 79 and 87 years) in the domains of verbal memory and abstract reasoning. This finding implicates APOE-є4 as a contributing risk factor for non-pathological cognitive decline.

Contrary to the findings that APOE-є4 is associated with decline in cognitively normal participants, Dik et al. (2000) found that the presence of APOE-є4 presence was not associated with memory decline in cognitively normal participants. Confirming this, Bunce and colleagues (Bunce et al., 2004) found that presence of APOE-є4 did not affect the rate of cognitive decline in pre-demented or non-demented individuals, or in pre-demented individuals relative to cognitively normal adults. Furthermore, Bunce et al. (2013) assessed eight-year cognitive change in a large sample of normal, community dwelling adults, including older adults aged 60-64 years at baseline. They reported no association between APOE-є4 and cognitive change in these older adults. Such findings suggest that the association between APOE-є4 and cognitive decline in cognitively normal older adults may be due to a higher probability of pre-clinical AD in APOE-є4 carriers (Batterham, Bunce, Cherbuin, & Christensen, 2013).

The above studies have focused predominantly on the role of APOE-ϵ4 in cognitively normal older adults and in pre-clinical AD. Other studies, however, have focused on the role of APOE-ϵ4 in the progression of AD and have confirmed that the APOE-ϵ4 allele is associated with a more rapid cognitive decline (Cosentino et al., 2008; Liu, Kanekiyo, Xu, & Bu, 2013). For example, Henderson et al. (1995) found an association between having the APOE-ϵ4 allele and cognitive decline in a population sample of adults aged 70 years and over. Similarly, Martins, et al. (2005) found that the APOE-ϵ4 allele strongly predicted the rate of cognitive decline in AD, with a dose-response relation. In other words, they found more rapid cognitive decline in patients with one ε4 allele, compared with those with none, and also in ε4/4 homozygotes compared with ε3/4 heterozygotes.

Exploring the role of APOE-ϵ4 in incident, prevalent, and diagnosed cases of AD, Consentino and colleagues demonstrated that presence of at least one ϵ4 allele was associated with cognitive decline in an incident population-based AD group. They concluded that the association between APOE-ϵ4 presence and cognitive decline was most significant in the earliest stages of AD (Cosentino et al., 2008).

APOE-ϵ4 has been implicated as a risk factor for cognitive decline in both normal cognitive ageing as well as in AD. However, findings related to its role in non-pathological ageing are mixed. The sum of the evidence suggests that APOE-ϵ4 may play a bigger role in the development of AD than in the progression of the disease; however, there is also evidence for its role in disease progression. The most recent research seems to favour the notion that APOE-ϵ4 exerts a larger effect on individuals who are already cognitively compromised compared to cognitively healthy controls, and that this effect is most prominent in early AD.

Psychosocial factor. The psychosocial factor described here is psychosocial stress.

Psychosocial stress. The experience of psychosocial stress is generally associated with poorer cognitive functioning (Neupert, Almeida, Mroczek, & Spiro, III; Peavy et al., 2007; Stawski et al., 2006). Psychosocial stress is also a risk factor for developing AD (Wilson et al., 2003). However, the association between psychosocial stress and cognitive decline is less well documented, and there is a need for prospective longitudinal studies to define the relationship between psychosocial stress and cognitive decline.

Epidemiological studies have found that chronic stress and stressful life events tend to accelerate cognitive decline. For instance, Peavy et al. (2009) explored the effects of chronic stress on memory decline in cognitively normal and mildly impaired older adults. This longitudinal study comprised 61 cognitively normal participants and 41 participants with MCI who completed repeated stress and cognitive assessments for up to 3 years. Higher event-based stress ratings were associated with faster cognitive decline, but only in MCI participants. In a later study, Peavy et al. (2012) examined the influence of chronic stress on dementia-related diagnostic change in older adults. At baseline, the participants were either cognitively normal or had a diagnosis of MCI. The researchers found that the conversion from MCI to dementia was associated with prolonged, highly stressful experiences. This association was not found in the conversion to MCI. These findings suggest that the influence of psychosocial stress may vary depending on the stage of cognitive impairment. The authors also propose that different mechanisms may exist in the conversion from normal cognition to MCI than in the conversion to dementia.

Some studies exploring the association between stress and cognitive decline have done so specifically in older adults who, at baseline, were cognitively normal. For example, Wilson et al. (2007) examined chronic distress and incidence of MCI in 1,256 older adults without cognitive impairment. During up to 12 years of follow-up, they found that the risk of MCI increased approximately 2% for each one unit increase on a distress scale. This study also found that individuals with a higher distress score were more likely to have a lower level of function in several cognitive domains at baseline. Furthermore, a higher distress score was associated with more rapid cognitive decline, particularly in the domain of episodic memory. Similarly, Vitaliano et al. (2005) investigated relationships between chronic stress and cognitive decline in cognitively healthy older adults to determine whether these relationships are mediated by psychophysiological factors. They compared 96 caregivers of spouses with AD with 95 similar non-caregiver spouses. The researchers hypothesized that the spouse caregivers, exposed to chronic caregiver-related stress, would show greater cognitive decline over the follow-up period than demographically similar non-caregiver spouses. Their data analyses detected a small but significant cognitive decline after two years in the caregivers, while the non-caregivers' cognitive functioning did not change.

The relationship between psychosocial stress and cognitive decline has been explored in more recent work and in larger samples than some of those previously

reported. For instance, Tschanz et al. (2012) explored the association between stressful life events and cognitive decline in late life, among 2,665 non-demented participants of the Cache County Memory Study. Participants completed a stressful life events questionnaire and were administered the MMSE. The MMSE was re-administered at follow-up visits 4 and 7 years later. General linear models assessed the association between stressful life event scores and cognitive functioning, and also explored the effects of age. Their results indicated that years of formal education modified the effect of number of stressful life events on the rate of cognitive decline; a more rapid rate of decline occurred among those with fewer years of education experiencing more stressful life events. Additionally, age modified the effect of negative stressful life events on the rate of cognitive decline; faster decline was observed in younger participants who experienced more negative stressful life events.

The findings discussed above indicate that chronic psychosocial stress is associated with cognitive decline in both cognitively normal and mildly cognitively impaired older adults. The general consensus seems to be that the effects of stress are greatest in those individuals who are already mildly cognitively impaired.

Sociodemographic factors. These include age and education.

Age. Age is a well-established risk factor for cognitive impairment (Kawas et al., 2000; Unverzagt et al., 2011), and has also been identified as a risk factor for increased rate of cognitive decline (Salthouse, 2009; Wilkosz et al., 2010). Brayne and colleagues (1995) examined cognitive decline in a sample of 1,111 older adults (all over the age of 75 years) who were administered the MMSE on two occasions separated by 28 months. Data analyses revealed a mean decline of 1.3 points in MMSE score and an increase in mean decline of MMSE score with increasing age. Similarly, in their observational, longitudinal study of rates of cognitive and functional decline in AD, Suh et al. (2004) found annual rates of decline of 2.3 MMSE points in AD patients. In this study, age was the only factor significantly related to more rapid annual decline; gender, duration of formal education, and duration of AD were not significant predictors of cognitive decline. In general, age confers significant risk for cognitive decline in older adults.

Education. The MacArthur Studies of Successful Ageing (e.g., Kubzansky, Berkman, Glass, & Seeman, 1998) identified an extensive group of psychological and physiological benefits of education in older adults. One of those benefits is better cognitive performance across the lifespan. In comparison, fewer years of education

have been associated with poorer performance on neuropsychological measures in older adults (Ganguli et al., 2010). Although such cross-sectional research demonstrates a clear relationship between education and cognitive performance, longitudinal data relating education to the rate of cognitive decline in older adults have been less convincing.

Alley, Suthers, and Crimmins (2007) investigated the relationship between education and age-associated rate of cognitive decline in a representative sample of community-dwelling American adults aged 70 years and older. This study consisted of four waves, between the years of 1993-2000; the same cognitive tests were administered to participants at all four waves. Their findings indicated that more years of education were associated with better initial cognitive performance and slower decline in mental status. These findings implicate the role of active cognitive reserve, i.e. those individuals with higher levels of education used more efficient ways to process cognitive tasks than those with lower levels of education. However, the results also demonstrated that there was greater absolute cognitive decline on the more complex verbal and working memory tasks among those individuals with the highest levels of education. These findings suggest that early-life experiences such as formal educational achievement play a role both in long-term cognitive functioning and in cognitive trajectories in old age.

The influence of education on long-term cognitive functioning is pertinent to diseases of old age such as AD. The relationship between level of education and the development of AD is well established (Barnes & Yaffe, 2011; Karp et al., 2004; Letenneur et al., 2000; O'Bryant et al., 2008; Sharp & Gatz, 2011). Fewer years of education are associated with an increased incidence of clinical AD, and have been noted as a risk factor for developing AD (Qiu et al., 2001).

While some studies have reported associations between fewer years of education and the development of AD, other studies (Schneider et al., 2012) have found faster rates of progression in AD patients with high levels (i.e. more years) of education (Hall et al., 2007; Scarmeas, Albert, Manly, & Stern, 2006; Stern, Tang, Denaro, & Mayeux, 1995; Teri, McCurry, Edland, Kukull, & Larson, 1995). In a sample of African-Americans, Unverzagt, Hui, Farlow, Hall, & Hendrie (1998) investigated the relationship between education and the degree of cognitive decline in mild dementia. They found that participants with dementia and a high level of education had greater cognitive decline, from estimated premorbid levels, than participants with dementia and

a low level of education. Similarly, Wilson et al. (2004) found that higher educational attainment was associated with a slightly increased rate of cognitive decline in a sample of 494 older adults with clinically diagnosed AD. In further support of this association, Scarmeas et al. (2006) reported that AD patients with higher levels of education experienced a faster rate of cognitive decline, and that this association occurred mainly in verbal fluency and memory. This association remained significant even after controlling for age, sex, ethnicity, differential baseline cognitive performance, depression, and vascular comorbidity.

A possible mechanism underlying this pattern of data is that AD patients with higher levels of education are better equipped, in terms of the cognitive reserve hypothesis and compensation techniques, for tolerating a heavier pathological load when the symptoms of clinical dementia emerge (Tucker & Stern, 2011). In other words, the pathological process of AD is more advanced when it first manifests, largely due to better compensatory mechanisms. In this instance, older persons with higher levels of education might make better use of their intact neuro-cognitive pathways to compensate for declining performance in regions that may be impaired. However, this compensation would only serve to slow cognitive decline temporarily; as the disease progresses into the later stages, more cognitive domains will become affected and start to deteriorate, leading to a more rapid rate of cognitive decline (Stern, 2009).

Some studies, employing multiple observations over longer periods of time, have found, however, that cognitive decline might not be moderated by formal educational attainment. For example, Wilson and colleagues (2009) confirmed that education is strongly associated with level of cognitive functioning as measured at any single point, but they found no linear association between education and rates of cognitive decline in community-dwelling older adults. Furthermore, using an analysis that allowed for nonlinearity in education, this study showed that rates of cognitive decline for those with average or high levels of education was slightly increased during the earlier follow-up years but decreased in the later follow-up years, compared to the rate for those with low levels of education. Based on longitudinal research findings, education seems less likely to play a role in cognitive decline than it does in cross-sectional assessments.

Consistent with the findings reported by Wilson et al. (2009), the Victoria Longitudinal Study reported that education was not related to age-associated cognitive decline over a 12 year study period (Zahodne et al., 2011). In a sample of 1014

participants aged 54-95 years and with an education range of 6-20 years, number of years of education was strongly related to cognitive functioning, but was unrelated to rates of change over time for any cognitive domain.

In summary, the extant literature seems to suggest the conclusion that there is a strong association between levels or years of formal educational attainment and risk for developing AD, i.e. those with fewer years of formal education are more likely to be at risk for AD, but the association between education and cognitive decline is not as strong.

Performing Longitudinal Studies of Ageing in LAMICs

The longitudinal studies reported in this literature review have emerged from high-income, predominantly Western, countries. To the best of my knowledge, there is no published longitudinal research of AD in African populations, apart from the studies performed in Nigeria with regards to incident dementia (for e.g., see Gureje, Ogunniyi, Kola, & Abiona, 2011). Kalaria and colleagues (2008) reviewed AD in developing countries, and described the difficulties associated with the measurement of cognitive decline in communities in LAMICs, particularly in the rural and more resource poor areas. Many of these difficulties are also present in cross-sectional studies. One such difficulty, which has been discussed in more detail in the *Introduction* section of Study 1, is the lack of standardized, culture-fair screening tools. Another obstacle to measure cognitive decline in developing countries is illiteracy which is reportedly high in developing countries such as in sub-Saharan Africa (Dowse & Ehlers, 2001; Umeora & Egwuatu, 2009). In addition, tracking cognitive decline in such contexts is often more difficult than in HICs as a result of migration (individuals from rural areas seeking employment often move to more urban areas) and lack of communication (frequently one cellular telephone is shared between several family members). Furthermore, when individuals are followed up, assessing changes in function may prove problematic because in some cultures, family members may take on the responsibilities of the older adults, leaving these adults with a limited range of activities to perform. It is difficult to assess changes in older adults' abilities to perform certain tasks when the activities that they do perform have become limited to a small number of simple tasks (Kalaria et al., 2008).

Despite the above-mentioned obstacles to performing longitudinal research in ageing in developing countries such as South Africa, this type of research is important because it may yield useful information regarding possible predictors of, or contributors to, cognitive change and/or decline in older adults from LAMICs. The ways in which these factors interact to increase risk for AD (and for cognitive decline in healthy older adults) in LAMICs might be different to that in HICs. For instance, individuals living in South Africa, particularly in less affluent rural areas, are more likely to experience traumatic life events and continuing psychosocial stress, with fewer resources to help them deal with this. Furthermore, although not yet formally studied, people living in LAMICs have a greater probability of experiencing negative events in early life (Kalaria et al., 2008) which may translate into an increased risk of AD in later life. So, if the predictors of, or contributors to, cognitive decline in older adults are different in LAMICs than in HICs, then this may provide insight into avenues for future preventative or intervention strategies.

On a more local level, there is also a lack of resources for diagnosing and treating AD in South African older adults. South Africa's ageing population will result in an increase in the prevalence and societal burden of cognitive impairment and various kinds of dementia, of which AD is likely to account for the majority. Thus, future intervention strategies might be guided by knowledge about risk factors for cognitive impairment and subsequent cognitive decline.

Summary

The literature demonstrates that there is variability around factors associated with cognitive decline. Findings pertaining to the physiological factors, namely cortisol and APOE-ε4, are contradictory. A common aspect in the literature regarding cortisol and APOE-ε4, however, is that their roles in AD appear to be most prominent in the preclinical and early stages of the disease. Psychosocial stress seems to confer an association with cognitive decline, although this association is greater in individuals who are already cognitively impaired, compared with controls. The evidence for age and education as contributors to cognitive decline is strong, with several studies reporting results in support of this.

Overall, longitudinal studies of AD are needed to develop a more conclusive and accurate understanding of the combined role that certain factors can play in the

progression of cognitive decline. Of particular interest in this LAMIC population longitudinal study is the impact of physiological (cortisol and APOE-ϵ4), psychosocial (psychosocial stress), and sociodemographic (age and education) factors on the progression of cognitive change and decline across a spectrum of healthy cognition to impaired cognition in AD.

Aims and Hypotheses

The purpose of this longitudinal study was to investigate cognitive change and cognitive decline over a period of 3 years across two samples: participants who were cognitively healthy at baseline measurement, and patients with AD. As noted in the literature review above, assessing participants longitudinally allows investigation of the predictive value of certain risk factors for cognitive change in healthy older adults, and for cognitive decline as AD progresses (Gomar, Bobes-Bascaran, Conejero-Goldberg, Davies, & Goldberg, 2011; Musicco et al., 2010; Wattmo, Wallin, Londos, & Minthon, 2011). The particular factors under consideration here were baseline psychosocial (self-perceived) stress and physiological stress (cortisol), as well as APOE-ϵ4 carrier status. I also considered the predictive value of age and education for determining cognitive change and decline in this sample of older South African adults, given that both of those variables were established by the Study 1 data analyses as factors associated with cognitive function in the sample.

After the baseline testing described in Study 1, participants were re-administered a cognitive test battery on an annual (12 ± 2 months) basis for 2 years. These re-assessments constituted the first follow-up (after one year; Time 1) and the second follow-up (after two years; Time 2).

I tested three hypotheses using the sociodemographic, physiological, and cognitive data collected at baseline and the physiological and cognitive data collected at Time 1 and Time 2. The first two hypotheses relate to psychosocial and physiological stress. *Hypothesis 1* stated that, across the entire sample, baseline levels of psychosocial stress (as measured by the PSS) and baseline levels of cortisol (log transformed values) would be significant predictors of cognitive change (as measured by CAMCOG-R total scores at each time point), even after taking into account individual differences in age, education, and APOE-ϵ4 carrier status. *Hypothesis 2* stated that participants with cognitive decline (as measured by a drop of one point or more on the MMSE) would

have higher baseline levels of psychosocial stress (as measured by the PSS) and higher baseline levels of cortisol (log transformed values), across the entire sample and relative to those participants who did not show cognitive decline. *Hypothesis 3* stated that participants who were APOE-ϵ4 carriers would be more likely to experience cognitive decline than participants who were not carriers.

Methods

Participants

Participants enrolled in the cross-sectional study were enrolled automatically in the longitudinal study if they were willing and/or able to continue their involvement in the research programme. Figure 10 illustrates the number of participants enrolled in the longitudinal study at the first and second follow-up visits. It also shows the number of participants who withdrew voluntarily, those controls who converted to MCI, those mild to moderate AD patients who declined to the severe stage of disease and who were therefore excluded from the follow-up visits, and those participants who did not have a follow-up visit. The latter, included participants who enrolled in the study at such a point that they were ineligible for a first or second follow-up assessment as data collection had ceased by the time they would have had the follow-up assessment. Participants were enrolled in the study even if they were going to have only the Baseline assessment because I wanted to have as large a group as possible at Baseline in order to have sufficient numbers to perform the regression model.

Participants involved in the longitudinal study included possible or probable AD patients (n_{AD} = 43 at first follow-up, n_{AD} = 19 at second follow-up). These participants had been recruited into the cross-sectional study from a variety of sources: a non-governmental agency nursing home located near Cape Town, Groote Schuur Hospital's Memory Clinic or geriatric outpatient clinic, and GP referrals. These patients had been diagnosed, prior to entering the study, as mild to moderate or possible or probable AD in terms of NINCDS/ADRDA criteria (McKhann et al., 1984). Most of these patients remained, across the follow-up period, in the mild to moderate stages of possible or probable AD, and were able to consent to procedures and to complete the cognitive tests. However, some of the AD patients enrolled in Study 1 withdrew or subsequently declined to a more severe stage of disease and were thus unable to be tested further (1 patient prior to the first follow-up and 6 patients prior to the second follow-up withdrew).

Control participants (n_{HC} = 52 at first follow-up, n_{HC} = 27 at second follow-up) were healthy, community-dwelling, independent volunteers. The control participants had been recruited into Study 1 via word-of-mouth advertising.

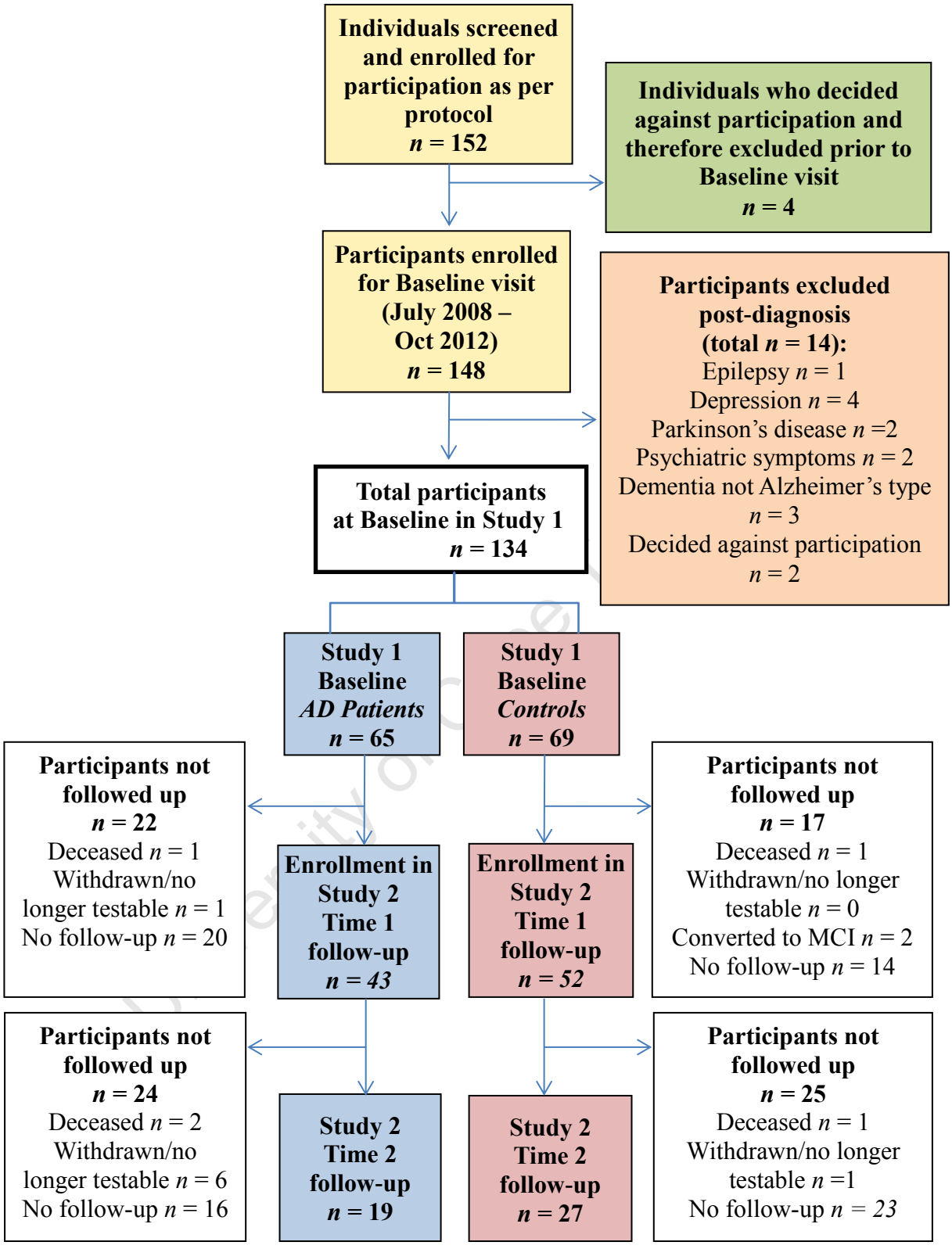


Figure 10. Diagram illustrating the number of participants (healthy controls and AD patients) enrolled in Study 2, as well as details relating to exclusion. Data collection and follow-up assessments ceased in October 2012. Some participants who were enrolled in the study during the later parts of 2010 and 2011 were not enrolled long enough to have a first and/or second follow-up assessment and therefore fall into the 'No follow-up' category.

Research Design and Setting

Standardized study procedures were conducted in the Division of Neurology at Groote Schuur Hospital, at a non-governmental agency nursing home, or at the participant's residence. Regardless of the venue, all participants were tested in an isolated, quiet room at similar times of day, between the hours of 09h00 and 11h30.

Materials

At the two follow-up visits, namely Time 1 and Time 2, I used a subset of the measures used in Study 1. The sociodemographic, psychosocial stress (LTE-Q and PSS), affective, behavioural and adaptive functioning questionnaires (DECO, BADLS, CD-RISC, and GDS) used in Study 1 were not re-administered at the follow-up visits.

Neuropsychological test battery. This battery included some of the tests used in Study 1 that have demonstrated good test-retest reliability and have been used to track cognitive decline, namely: the CAMCOG-R, MMSE, TMT, and CLOX. Further descriptions of these instruments, including details regarding their psychometric properties and previous use in South Africa, can be found in the Methods section of Study 1. The TPT was not re-administered at the follow-up visits as its test-retest properties have not yet been demonstrated.

Physiological measures. At each follow-up visit I administered *Sarstedt Salivette® Cortisol* devices to participants so that they could collect saliva samples from which cortisol levels would be determined. Further details relating to the salivettes are in the Methods section of Study 1.

Procedures.

Figure 11 presents an outline of the procedure for those participants involved in Study 2. The follow-up procedure was identical for both the first and second follow-up visits. Approximately 1 and 2 years (± 2 months) after participants' initial baseline visit, the researcher contacted the participants and their family members to arrange a follow-up appointment for the participant and his/her informant in the Division of Neurology at GSH. The day before the test session, the researcher contacted the participant and/or the informant to remind them of their GSH appointment. This session was arranged such that the participants were tested at the same times of day as for the baseline assessments, between the hours of 09h00 and 11h30. On the day of the testing session,

when the participant and informant arrived at GSH, they were met by the researcher and escorted to the testing venue in the Division of Neurology.

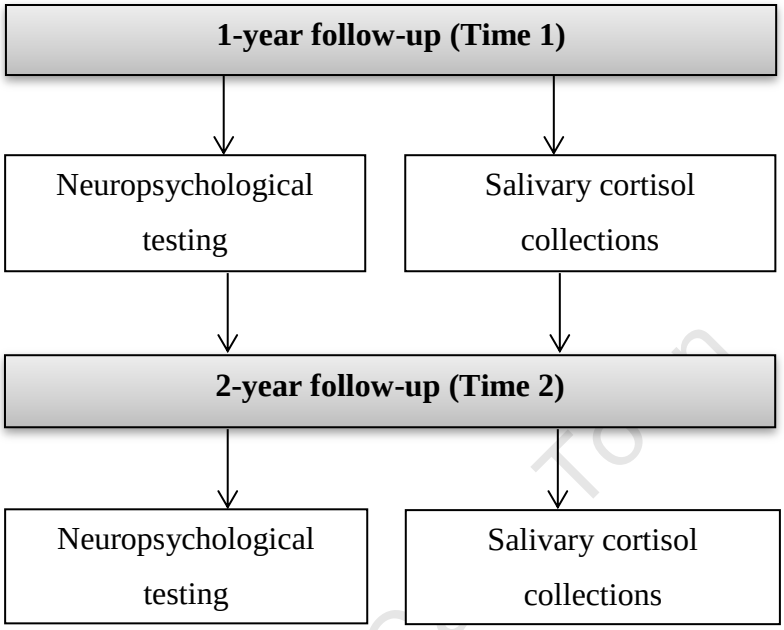


Figure 11. Diagram of participant study procedure through the first and second follow-up visits.

Neuropsychological testing. During the testing session the researcher administered the neuropsychological test battery (i.e. CAMCOG-R, including the MMSE, TMT, and CLOX). The duration of each follow-up neuropsychological test session usually lasted between 30 and 60 minutes.

At the end of the testing session, the researcher again provided the participant and/or the informant with two sets of salivettes and instructions for using them. For those participants with memory problems, the instructions and salivettes were given to the informant, who was also instructed how to assist the participant in obtaining the saliva sample. Participants were required to collect their saliva samples at 09h00 on two mornings in succession. Once both saliva samples had been taken, the participant, or the informant, called the research team to let us know that the samples were ready for collection. After the researcher collected the salivettes, they were stored in a freezer at -20°C at GSH before being taken for analysis at the hospital's Chemical Pathology Laboratory, where a standard assay was performed to determine salivary cortisol levels.

Analytical procedures for saliva samples. Once a batch of salivettes had been collected and stored in a freezer at -20°C, the researcher took them to the hospital's Chemical Pathology Laboratory, where a standard assay was performed to determine salivary cortisol levels.

Ethical and Safety Considerations

All study procedures were approved by the Research Ethics Committees of the University of Cape Town's Department of Psychology and the Faculty of Health Sciences (REC REF 346/2008). The study was conducted according to the ethical guidelines and principles of the International Declaration of Helsinki, the South African Guidelines for Good Clinical Practice and the MRC Ethical Guidelines for Research. All participants were provided with thorough and detailed written and verbal information about the study; their anonymity was assured and they were informed of their right to withdraw from the study at any given point, without prejudice. Participants were informed about all the relevant study procedures and what their role in the study would entail.

Data Management and Statistical Analyses

I sorted and cleaned the data and checked for any missing items. I used Statistica 10 or SPSS version 19.0 for all analyses. For measures taken at Time 1 and Time 2, I performed descriptive statistical analyses of all the data and calculated measures of central tendency (mean and median) and dispersion (range, standard deviation, and variance) for all variables. I also constructed boxplots for all the continuous predictor variables (age, education, psychosocial stress, and cortisol) in order to detect outliers that may have influenced the measures of central tendency. For the inferential statistical analyses that followed, I set the alpha level at .05. Where necessary (i.e., where assumptions of sphericity were not satisfied), I used Greenhouse-Geisser corrected degrees of freedom. I used Cohen's d or η_p^2 as estimates of the effect sizes for parametric data; Cohen's r as an estimate of effect size for non-parametric data; and φ as an estimate of effect size for the chi-square (χ^2) analyses.

Deriving outcome variables. Statistical analyses assessed predictors of cognitive change and of cognitive decline. The reason for exploring both cognitive change and cognitive decline is that cognitive change over time does not necessarily

denote decline; especially in controls, scores at the follow-up assessments could have remained constant, or even improved slightly because of practice effects or reduced anxiety due to increased familiarity with the assessment situation.

Cognitive change was defined, simply, as change in CAMCOG-R total score across the three CAMCOG-R administrations. Hence, this construct measures cognitive performance along a continuum.

In contrast, to assess *cognitive decline*, I compared groups of participants who declined against those who did not. To define these groups, I first compiled a list of participants whose MMSE score decreased by 1 point or more from Baseline to Time 1, or by 2 points or more from Baseline to Time 2. As a reminder, the sample size at Baseline was, $N = 134$; $n_{HC} = 69$, n_{AD} = patients 65. Each participant who had cognitive data for all three time points ($N = 43$; $n_{HC} = 27$, $n_{AD} = 19$) therefore had two cognitive decline scores: one for Time 1 score subtracted from Baseline score, and one for Time 2 score subtracted from Baseline score. Those participants who dropped out of the study before Time 2 had only one cognitive decline score (Baseline minus Time 1). The sample size at Time 1 was, $N = 95$; $n_{HC} = 52$, $n_{AD} = 43$. Those participants who dropped out of the study before Time 1 did not have a cognitive decline score. For each of Time 1 cognitive decline (i.e., Baseline minus Time 1) and Time 2 cognitive decline (i.e., Baseline minus Time 2), I divided participants into two groups: those who declined (Decliners) and those who did not decline (Non-decliners) between the two measurement points.

The choice to define Time 1 cognitive decline as a decrease of ≥ 1 point per year on the MMSE has precedent in several previously published studies (Kalmijn et al., 1999; Ng, 2008; Niti, Yap, Kua, & Ng, 2009; Kalmijn, Janssen, Pols, Lamberts, & Breteler, 2000; Volpato et al., 2002). A year-to-year drop of ≥ 1 point on the MMSE corresponds to a drop of ≥ 2 points over 3 or more years of follow-up, and represents considerable cognitive decline (Ng, Feng, Niti, Kua, & Yap, 2008).

Inferential statistical analyses. Before testing the three hypotheses listed above, I sought to characterise the sample by conducting several statistical analyses of between-group differences in demographic and cognitive variables at Time 1 and Time 2. I used either *t*-tests or Mann-Whitney *U* tests, depending on whether the data met the assumptions underlying parametric statistical analyses.

Testing Hypothesis 1. A general linear model with repeated measures (GLM-RM) examined whether psychosocial stress and cortisol predicted cognitive change

across the three measurement points, taking into account age, education, and APOE-ϵ4. I entered Time (Baseline; Time 1; Time 2) as the within-subjects factor, CAMCOG-R total score at each measurement point as the outcome variable, and age (in years), education (number of completed years), APOE-ϵ4 carrier status (with or without), log transformed cortisol values, PSS scores for psychosocial stress, and group status (healthy control versus AD patient) as predictors. The first three variables were included in this model based on their demonstrated associations with cognitive functioning (in Study 1 and in previously published studies), and because, in the current sample, there were significant between-group differences for each of these variables.

Testing Hypothesis 2. An optimal solution for examining whether psychosocial stress and cortisol predicted cognitive decline would have been to perform one large regression or general linear model, including as predictors: age, education, APOE-ϵ4 carrier status, cortisol level, and PSS scores; and as the outcome variable, cognitive decline (from Baseline to Time 1, or from Baseline to Time 2). However, given the small numbers at Time 1 and especially at Time 2, there was insufficient power to include all of these predictors in one model. For example, a model including age, education, APOE-ϵ4, cortisol, and PSS scores as predictors and Baseline to Time 1 cognitive decline as the outcome variable, had insufficient power (with $N = 38$) to detect a medium-sized effect. A post-hoc power analysis for this model indicated actual power of 0.06, with ideal power ($1 - \beta$) set at .80 and $\alpha = .05$, two-tailed, and a small effect size of 0.01.

As the next best solution for testing Hypothesis 2, I divided participants into two groups based on whether or not they had demonstrated cognitive decline from Baseline to Time 1 and from Baseline to Time 2. I then performed *t*-tests to determine whether there were between-group (Decliners versus Non-decliners) differences for psychosocial stress and cortisol.

Testing Hypothesis 3. Two separate χ^2 tests of contingency tested this hypothesis. In each, APOE-ϵ4 carrier status (with or without) was one dichotomous variable and decline status (yes or no) was the other. The only difference between the two tests was that the first described the contingency between the variables when decline was defined as a decrease in MMSE score of ≥ 1 point from Baseline to Time 1, and the second described the contingency between the variables when decline was defined as a decrease in MMSE score of ≥ 2 points from Baseline to Time 2.

Exploratory analyses. As noted earlier, each participant provided two consecutive samples of salivary cortisol at Baseline, at Time 1, and at Time 2. Because previous studies suggested that cortisol levels increased as people age (see, e.g., Deuschle et al., 1997; Otte et al., 2005; Vgontzas et al., 2003), I was interested in analysing the changes in salivary cortisol levels over time in this study sample.

I took the average value of each of the two samples from each visit to represent cortisol levels at, respectively, Baseline, Time 1, and Time 2. The raw scores of those average values were not normally distributed, however. Hence, I performed a log transformation of these data, and used those log transformed values in the analyses described next. I used a GLM-RM to examine how cortisol levels changed in the sample across three measurement points. In this model, I entered Time (Baseline, Time 1, Time 2) as the within-subjects predictor, Group (controls versus AD patients) and age as between-subjects predictors, and the three cortisol levels as outcome variables.

Results

The results are presented under three broad headings: Sample Characteristics, Hypothesis Testing, and Exploratory Analyses. The first section, which includes Tables 15-20, presents the demographic and cognitive characteristics of the Time 1 and Time 2 sub-samples (recall that not every participant for whom I obtained data at Baseline returned at Time 1, and not every Time 1 participant returned at Time 2). For each of Time 1 and Time 2, I first present the sample's demographic characteristics and then I present the cognitive data. I then present data pertaining to those participants who remained in this study through Time 2, those who withdrew, and those who died (Tables 20-21).

The second section presents results pertaining to tests of Hypotheses 1-3. The third section presents results of the exploratory analyses related to cortisol levels, as described above.

Sample Characteristics at Time 1 and Time 2

Demographic and Cognitive Data. Table 16 shows the demographic data for the Time 1 participants. Consistent with the demographic data for the Baseline sample (N = 134; $n_{\text{AD patients}}$ = 65, n_{HC} = 69) presented in Study 1, there were significant between-group differences with regard to age, distribution of race, education, and household income. AD patients were older, had fewer years of education, and had a lower monthly income. Regarding APOE-ϵ4 carrier status, which was measured at baseline, there was a strong trend toward a significant between-group difference: Of the participants who remained in the study at Time 1, most AD patients had the ϵ4 allele and most controls did not.

Table 17 shows, for the Time 1 participants, descriptive statistics and between-group comparisons for the CAMCOG-R (total score and subscale scores), MMSE, TMT, and CLOX. Because data were not normally distributed, I present medians and inter-quartile ranges rather than means and standard deviations. Consistent with results from analyses reported in Study 1 for the Baseline sample, these results show that, at Time 1, AD patients had significantly poorer cognitive functioning (both overall and within specific domains) than controls

Table 16
Time 1: Sample Demographic Data (N = 95)

Variable	Group: Controls (n = 52)	Group: AD Patients (n = 43)	*df*	t / χ^2	*p*	ESE
Age	72.35 (8.23)	77.19 (8.55)	93	-2.80[a]	.006**	0.58
Sex (M:F)	12:40	12:31	1	0.29[b]	.59	-0.06
Race (W:B:C:I)	28:1:23:0	4:1:37:1	1	21.61[b]	< .001***	0.48
Education (years)	13.87 (4.51)	8.72 (3.02)	93	6.39[a]	< .001***	1.34
Handedness (Right:Left)	47:5	42:1	1	2.11[b]	.15	-0.15
Body Mass Index	28.00 (6.44)	26.35 (5.47)	78	1.21[a]	.23	0.28
APOE-ϵ4 (With:Without)	20:31	25:17	1	3.80[b]	.05	-0.20
Monthly household income < ZAR2500:≥ ZAR2500	10:42	37:6	1	42.04[b]	< .001***	0.67

Note. For the variables *Age, Education,* and *Body Mass Index,* means are presented with standard deviations in parentheses. APOE-ϵ4 = apolipoprotein ϵ4. For the variable *Race,* W = White, B = Black African, C = Coloured, I = Indian. [a]Test statistic for *t*-test. [b]Test statistic for Mann-Whitney *U* test. ESE = effect size estimate; in this case, either Cohen's *d* for *t*-tests or φ for χ^2 tests.
*p < .05. **p < .01. ***p < .001.

Table 17
Time 1: Sample Cognitive Data (N = 95)

		Group				
	Max. Attainable Score	Controls (n = 52)	AD Patients (n = 43)	Z	p	ESE
CAMCOG-R	105	94.00 (7.00)	63.50 (24.00)	8.22	< .001***	0.84
Memory	27	22.50 (4.00)	9.00 (8.00)	8.08	< .001***	0.83
Orientation	10	10.00 (0.00)	7.00 (5.00)	6.96	< .001***	0.71
Language	30	27.00 (2.00)	22.00 (6.00)	7.01	< .001***	0.72
Attention	7	7.00 (1.00)	3.00 (4.00)	5.82	< .001***	0.60
Calculation	2	2.00 (0.00)	1.00 (1.00)	4.81	< .001***	0.49
Praxis	12	11.00 (2.00)	9.00 (3.00)	5.34	< .001***	0.55
Abstract Thinking	8	7.00 (2.00)	4.00 (4.00)	6.52	< .001***	0.67
Perception	9	8.00 (2.00)	5.00 (2.00)	6.58	< .001***	0.68
Learning	17	14.00 (2.00)	7.00 (6.00)	7.42	< .001***	0.76
MMSE	30	29.00 (2.00)	20.50 (6.00)	7.97	< .001***	0.82
TMT-A	90 seconds	42.00 (16.00)	90.00 (106.00)	-6.99	< .001***	-0.72
TMT-B	300 seconds	93.50 (35.50)	300.00 (66.00)	-7.38	< .001***	-0.76
CLOX 1	15	13.00 (2.00)	10.00 (4.00)	5.69	< .001***	0.58
CLOX 2	15	14.00 (1.00)	13.00 (3.00)	-2.53	< .001***	-0.26

Note. Medians are presented with interquartile ranges in parentheses. Z = test statistic for Mann-Whitney U test. CAMCOG-R= Cambridge Cognitive Examination-Revised; MMSE = Mini-Mental State Examination. TMT-A = Trail Making Test (Part A); TMT-B = Trail Making Test (Part B); CLOX 1 = Executive Clock Drawing Task (Part 1); CLOX 2 = Executive Clock Drawing Task (Part 2). For both TMT trials, the outcome variable is time, in seconds. For each between-group comparison, degrees of freedom = 93. Z = Test statistic for Mann-Whitney U test. ESE = effect size estimate; in this case, Cohen's r (for non-parametric data).
*p < .05. **p < .01. ***p < .001.

Table 18 shows the demographic data for the Time 2 participants. Significant differences between the groups were found for education and income, where the AD patients had fewer years of education and a lower level of income.

Table 19 shows, for the Time 2 participants, the descriptive statistics and between-group comparisons for the CAMCOG-R (total score and subscale scores), MMSE, TMT, and CLOX. Because data were not normally distributed, I present medians and inter-quartile ranges rather than means and standard deviations. Consistent with results from analyses reported in Study 1 for the Baseline sample, and with the results from Time 1, these results show that AD patients had significantly poorer cognitive functioning (both overall and within specific domains) than controls.

Table 18
Time 2: Sample Demographic Data (N = 46)

	Group					
	Controls (n = 27)	AD Patients (n = 19)	*df*	t / χ^2	*p*	ESE
Age	73.85 (9.09)	75.89 (9.62)	44	-0.73[a]	.47	0.22
Sex (M:F)	7:20	8:11	1	1.33[b]	.25	-0.17
Race (W:B:C:I)	9:0:18:0	2:0:16:1	1	4.31[a]	.23	0.31
Education (years)	13.04 (4.75)	9.26 (3.25)	44	2.30[b]	.004**	0.93
Handedness (Right:Left)	2:25	1:18	1	.08[b]	.77	0.04
APOE-ϵ4 (With:Without)	9:18	11:8	1	2.74[b]	.10	-0.24
Body Mass Index	27.65 (5.59)	26.69 (5.95)	41	.05[a]	.60	1.14
Monthly household income < ZAR2500:≥ ZAR2500	6:21	18:1	1	17.17[b]	<.001***	-0.61

Note. For the variables *Age*, *Education*, and *Body Mass Index*, means are presented with standard deviations in parentheses. For the variable *Race*, W = White, B = Black African, C = Coloured, I= Indian. [a]Test statistic for *t*-test. [b]Test statistic for Mann-Whitney *U* test. ESE = effect size estimate; in this case, either Cohen's *d* for *t*-tests or φ for χ^2 tests.
*p < .05. **p < .01. ***p < .001.

Table 19
Time 2: Sample Cognitive Data (N = 46)

		Group				
	Max. Attainable	Controls (n = 27)	AD Patients (n = 19)	Z	p	*ESE*
CAMCOG-R	105	94.00 (5.00)	68.00 (27.00)	5.66	< .001***	0.83
Memory	27	22.00 (2.00)	7.00 (9.00)	5.57	< .001***	0.82
Orientation	10	10.00 (0.00)	8.00 (3.00)	3.90	< .001***	0.57
Language	30	27.00 (2.00)	22.00 (7.00)	4.84	< .001***	0.71
Attention	7	7.00 (1.00)	3.00 (4.00)	3.16	< .001***	0.47
Calculation	2	2.00 (0.00)	1.00 (1.00)	3.22	< .001***	0.47
Praxis	12	11.00 (1.00)	9.00 (5.00)	2.93	.003**	0.43
Abstract Thinking	8	7.00 (1.00)	6.00 (5.00)	2.78	.005**	0.40
Perception	9	8.00 (1.00)	5.00 (2.00)	3.98	< .001***	0.59
Learning	17	15.00 (2.00)	5.00 (8.00)	5.14	< .001***	0.76
MMSE	30	28.00 (2.00)	22.00 (8.00)	5.24	< .001***	0.77
TMT-A	90 seconds	42.00 (24.00)	72.00 (54.00)	-3.30	< .001***	-0.49
TMT-B	300 seconds	118.00 (75.00)	300.00 (150.00)	-3.76	< .001***	-0.56
CLOX 1	15	13.00 (1.00)	10.50 (4.00)	3.52	< .001***	0.52
CLOX 2	15	14.00 (2.00)	11.50 (4.00)	3.78	< .001***	0.56

Note. Medians are presented with interquartile ranges in parentheses. Z = test statistic for Mann-Whitney U test. CAMCOG-R= Cambridge Cognitive Examination-Revised; MMSE = Mini-Mental State Examination. TMT-A = Trail Making Test (Part A); TMT-B = Trail Making Test (Part B); CLOX 1 = Executive Clock Drawing Task (Part 1); CLOX 2 = Executive Clock Drawing Task (Part 2). For both TMT trials, the outcome variable is time, in seconds. For each between-group comparison, degrees of freedom = 44. Z = Test statistic for Mann-Whitney U test. ESE = effect size estimate; in this case, Cohen's r (for non-parametric data).
*p < .05. **p < .01. ***p < .001.

Table 20 shows between-group comparisons for the AD patients who remained in the study through Time 2 (the Remained group) and those who withdrew/were no longer testable/had died either before Time 1 or before Time 2 (the Withdrew group). This analysis does not include controls because there were so few who withdrew/were no longer testable/had died (n = 5). This analysis also does not include those AD patients who were not enrolled in the study long enough to have had follow-up measurements. Patients in the Withdrew group were significantly older and had lower baseline MMSE and CAMCOG-R scores than those in the Remained group.

Table 20
Between-Group Differences at Baseline for AD Patients who Remained in the Study and those who Withdrew (N = 29)

	Group					
	Remained (n = 19)	Withdrew (n = 10)	*df*	*t* / χ2	*p*	ESE
Age	73.89 (9.62)	79.40 (8.13)	27	1.54	.14	0.62
Sex (M:F)	8:11	1:9	1	3.16	.08	0.33
Education	9.26 (3.25)	7.70 (2.21)	27	-1.36	.19	0.56
Body Mass Index	26.69 (5.95)	25.34 (4.24)	21	-0.54	.60	0.26
APOE-ϵ4 (With:Without)	11:8	6:4	1	0.01	.91	-0.02
CAMCOG-R	69.47 (11.17)	57.00 (19.40)	27	-2.21	.04*	0.78
MMSE	22.21 (3.36)	17.80 (5.41)	27	-2.72	.01*	0.98
PSS	18.47 (9.02)	23.10 (8.23)	27	1.35	.19	0.54
Cortisol	0.65 (0.37)	0.69 (0.37)	17	-0.23	.83	0.11

Note. The group of AD patients who withdrew also includes patients who were no longer testable or who had died. Means are presented with standard deviations in parentheses for parametric data. All the variable measurements are from the Baseline assessment. Age = years. Education = years of completed education. CAMCOG-R = Cambridge Cognitive Examination-Revised; MMSE = Mini-Mental State Examination; PSS = Perceived Stress Scale – measure of psychosocial stress. Cortisol is the average of the two cortisol collections at Baseline; this is the log transformed data. ESE = effect size estimate; in this case, Cohen's *d*.
*p < .05. **p < .01. ***p < .001.

Table 21 presents data on those participants (n = 5; 2 controls and 3 AD patients) who died during the study. The observed z-scores indicate that most of these participants were older, and had fewer years of education, than their respective group means. Except for participant D5, scores for cognition (CAMCOG-R and MMSE) and general functioning (DECO) for these participants were all below their respective group means, indicating a relatively high degree of impairment. However, the magnitude of z-

scores for each variable and for each participant varies substantially and so did not suggest that any particular constellation of cognitive and functional characteristics distinguished individuals who died during the study.

Table 21

Baseline Data Z-scores for Participants Who Died during the Study

	Group	Age	Education	BMI	CAMCOG-R	MMSE	Cortisol	PSS	DECO
D1	Control	2.01	-0.36	-.10	-1.30	-1.43	-0.58	-1.22	0.59
D2	Control	3.28	-1.20	-	-1.68	-2.65	-	0.88	-2.00
D3	Patient	0.50	-0.47	-0.77	-1.54	-1.16	-1.08	0.42	-0.49
D4	Patient	1.64	-1.40	1.42	-1.77	-2.05	0.48	0.55	-0.73
D5	Patient	0.74	-0.47	0.74	0.22	0.39	-	-0.67	0.24

Note. *Z*-scores are based on the separate group means and standard deviations for controls and AD patients. BMI = Body Mass Index; CAMCOG-R = Cambridge Cognitive Examination-Revised; MMSE = Mini-Mental State Examination. PSS = Perceived Stress Scale – measure of psychosocial stress. DECO = Deterioration Cognitive Observee – measure of cognitive and physical functioning. If the *z*-score is positive, its corresponding raw score is above the mean; if the *z*-score is negative, its corresponding score is below the mean.

***Hypothesis 1*: Psychosocial Stress, Cortisol, and Cognitive Change**

To investigate the extent to which PSS scores and cortisol levels (both as measured at Baseline; log transformed data) contributed to cognitive change (as measured by CAMCOG-R total score at Baseline, Time 1, and Time 2) I performed a GLM-RM. This model also included age, education, APOE-ϵ4 carrier status, and group status (healthy control versus AD patient) as predictors. The analysis included data from the 46 participants who completed assessment at the three measurement points ($n_{HC} = 27$, $n_{AD} = 19$).

Table 22 summarises the data on which the analysis was conducted. Figure 12 shows, for each group separately, changes in CAMCOG-R total score from Baseline to Time 1 to Time 2. As the Table and Figure show, the mean CAMCOG-R scores of controls remained fairly consistent across the three time points. Figure 12, panel (a) shows the mean CAMCOG-R total scores for healthy controls and AD patients at Baseline, Time 1, or Time 2. In other words, panel (a) includes data for all participants who had at least a Baseline CAMCOG-R score; some did not have data for all three measurement points. Figure 12, panel (a) suggests that the mean scores in AD patients decreased from Baseline to Time 1, and increased slightly from Time 1 to Time 2. This increase is likely to have been an artifact of selective attrition: Some of the patients with the lowest scores at Baseline or at Time 1 dropped out before the Time 2 follow-up. As a result, the mean AD patient score at Time 2 is higher than that at Time 1 increase, but this estimate of functioning is likely based on a healthier sample than that measured at Baseline and at Time 1. This inference is supported by the data presented earlier (see Table 20), which shows that the AD patients who died during the study had significantly lower Baseline CAMCOG-R total and MMSE scores than their group means. Furthermore, the AD patients who were no longer involved in the study at Time 2 (due to voluntary withdrawal, disease severity, or death) tended to have lower baseline MMSE, CAMCOG total, and DECO scores than those patients who remained in the study (see Table 20).

Figure 12, panel (b), therefore provides a more accurate reflection of the trajectory of cognitive functioning across time in this sample. The data presented in that figure are based only on scores from the controls and AD patients who had complete cognitive data at all three measurement points. The figure shows that, whereas the mean score for controls remained largely consistent, that for AD patients decreased over time.

As expected, the GLM-RM detected significant main effects of age, $F(1, 36) = 5.65$, $p = .02$, $\eta_p^2 = .14$, education, $F(1, 36) = 6.33$, $p = .02$, $\eta_p^2 = .15$, and of group, $F(1, 36) = 65.78$, $p < .001$, $\eta_p^2 = .65$ on cognitive change. The analysis also detected a significant time x group interaction, $F(1.59, 57.09) = 9.71$, $p = .001$, $\eta_p^2 = .21$; this interaction is depicted in Figure 12, panel (b).

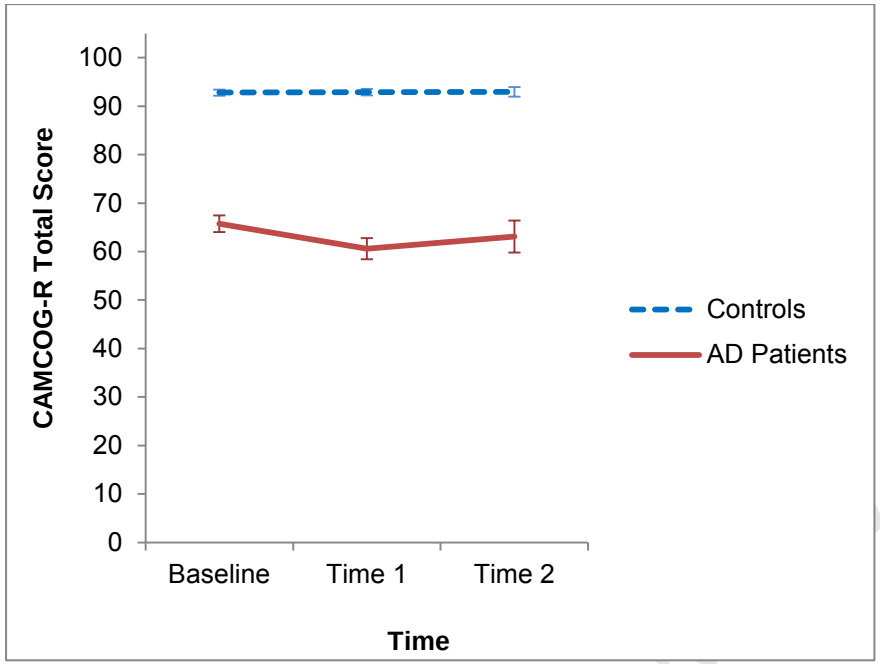
The analysis detected no significant main effect of APOE-ϵ4 carrier status, $F(1, 36) = 1.44$, $p = .24$, $\eta_p^2 = .04$, cortisol levels, $F(1, 36) = 0.29$, $p = .59$, $\eta_p^2 = .008$, or PSS score, $F(1, 36) = 0.08$, $p = .78$, $\eta_p^2 = .002$. It also detected no other significant two-way interactions involving time, each $F(1.46, 54.14) < 1.30$, each $p > .30$, each $\eta_p^2 < .04$.

Table 22
Descriptive Data at Baseline for Predictor Variables in the GLM-RM for Cognitive Change

	Total (N = 46)	Controls (n = 27)	AD Patients (n = 19)
Age	72.51 (9.01)	71.67 (9.09)	73.94 (8.96)
Education	11.86 (4.66)	13.33 (4.67)	9.38 (3.52)
APOE-ϵ4 (With:Without)	19:27	9:18	10:9
Cortisol	0.68 (0.33)	0.69 (0.33)	0.65 (0.37)
PSS	16.69 (8.38)	16.67 (8.77)	17.00 (7.97)
CAMCOG-R Total Score			
Baseline	82.98 (13.17)	90.78 (5.49)	69.81 (11.80)
Time 1	83.26 (14.78)	92.30 (4.51)	68.00 (13.45)
Time 2	82.37 (16.59)	92.94 (6.12)	60.71 (14.02)

Note. For all variables, means are presented with standard deviations in parentheses. APOE-ϵ4 = apolipoprotein ϵ4. PSS = Perceived Stress Scale – measure of psychosocial stress. CAMCOG-R = Cambridge Cognitive Examination-Revised. Data are presented for all three measurements of the CAMCOG-R.

(a)



(b)

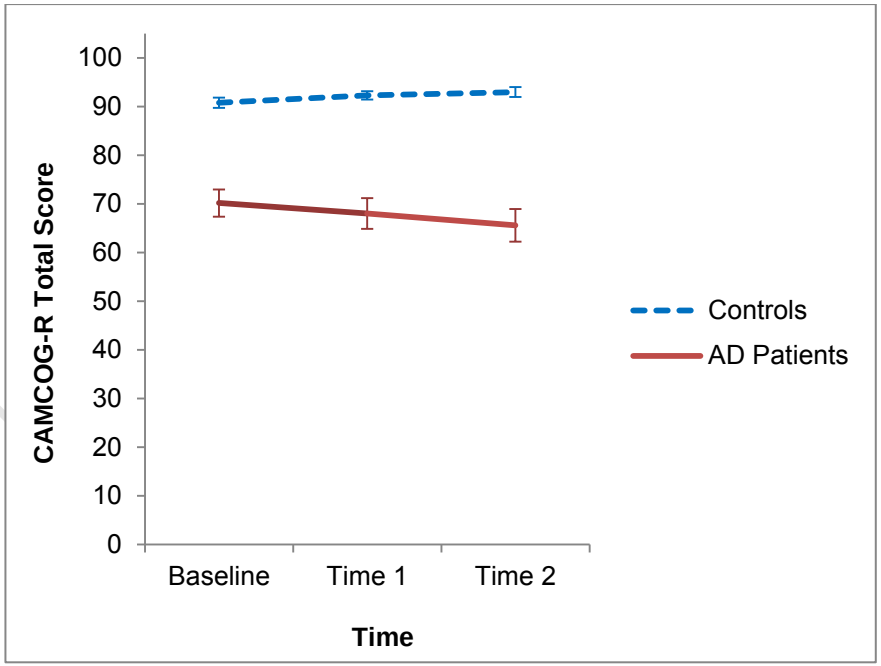


Figure 12. Panel (a) shows mean CAMCOG-R total scores, with standard error bars, for participants who completed assessment at Baseline (n_{HC} = 69, n_{AD} = 65), at Time 1 (n_{HC} = 52, n_{AD} = 42), or at Time 2 (n_{HC} = 27, n_{AD} = 19). Panel (b) shows mean CAMCOG-R total scores, with standard error bars, for only those participants who completed assessment at all three measurement points (n_{HC} = 27, n_{AD} = 19).

***Hypothesis 2*: Psychosocial Stress, Cortisol, and Cognitive Decline**

Tables 23 and 24 show results of the between-group comparisons investigating differences between the Decliners and Non-decliners from Baseline to Time 1 and from Baseline to Time 2, respectively. Regarding Time 1 cognitive decline, there were no significant between-group differences at the Bonferroni-corrected *p*-value (.01), although age ($p = .07$) and PSS scores for psychosocial stress ($p = .09$) tended toward significance. Results showed that there was no significant difference in baseline cortisol levels for those who declined and those who did not decline. Regarding Time 2 cognitive decline, there were no significant differences for any of the variables, namely age, education, cortisol, and PSS.

Table 23
Between-group Comparisons for Decliners and Non-decliners at Time 1 Cognitive Decline (N = 95)

	Group					
	Decliners	Non-decliners				
Variable	($n = 41$)	($n = 54$)	*df*	*t*	*p*	ESE
Age	75.46 (7.88)	72.25 (9.03)	94	-1.82	.07	0.38
Education	11.59 (4.59)	11.62 (4.76)	94	0.03	.97	0.01
Cortisol	.81 (.32)	.80 (.34)	87	-.16	.87	0.03
PSS	20.17 (7.45)	17.33 (8.46)	94	-1.71	.09	0.36

Note. For all variables, means are presented with standard deviations in parentheses. A Bonferroni correction was applied as multiple t-tests were used. All the variable measurements are from the Baseline assessment. Age = years. Education = years of completed education. Cortisol is the average of the two cortisol collections at Baseline; this is the log transformed data. PSS = Perceived Stress Scale – measure of psychosocial stress. ESE = effect size estimate; in this case, Cohen's *d*.
*$p < .05$. **$p < .01$. ***$p < .001$.

Table 24
Between-group Comparisons for Decliners and Non-decliners at Time 2 Cognitive Decline (N = 46)

	Group					
	Decliners	Non-decliners				
Variable	(*n* = 32)	(*n* = 14)	*df*	*t*	*p*	ESE
Age	73.43 (9.91)	72.22 (9.13)	44	-0.40	.69	0.13
Education	11.29 (4.49)	11.81 (4.49)	44	0.36	.72	0.11
Cortisol	0.70 (0.30)	0.70 (0.34)	43	0.01	.99	0.00
PSS	19.43 (8.20)	16.00 (7.91)	43	-1.33	.19	0.43

Note. For all variables, means are presented with standard deviations in parentheses. A Bonferroni correction was applied as multiple *t*-tests were used. All the variable measurements are from the Baseline assessment. Age = years. Education = years of completed education. Cortisol is the average of the two cortisol collections at baseline; this is the log transformed data. PSS = Perceived Stress Scale – measure of psychosocial stress. ESE = effect size estimate; in this case, Cohen's *d*.
**p* < .01. ***p* < .001.

Hypothesis 3: Apolipoprotein ϵ4 and Cognitive Decline

Tables 25 and 26 show the contingency tables upon which the analyses here were based. For both Time 1 and Time 2 cognitive decline, the analyses showed that participants who were APOE-ϵ4 carriers were not more likely to decline than participants who were not, $\chi^2(1) = 1.75$, $p = .19$, $\varphi = .14$, and $\chi^2(1) = 0.94$, $p = .33$, $\varphi = .15$, respectively.

Table 25
Contingency Table for Time 1 Cognitive Decline and APOE ϵ4 Carrier Status (N = 93)

	APOE ϵ4+	APOE ϵ4-
Decliners	23	18
Non-decliners	22	30

Note. APOE-ϵ4 = apolipoprotein ϵ4. Decliners = those participants who declined by ≥ 1 point on the Mini-Mental State Examination (MMSE). Non-Decliners = those participants whose MMSE scores either remained the same or increased over time.

Table 26

Contingency Table for Time 2 Cognitive Decline and APOE ϵ4 Carrier Status (N = 43)

	APOE ϵ4+	APOE ϵ4-
Decliners	6	6
Non-decliners	11	20

Note. APOE-ϵ4 = apolipoprotein ϵ4. Decliners = those participants who declined by ≥ 2 points on the Mini-Mental State Examination (MMSE). Non-Decliners = those participants whose MMSE scores either remained the same or increased over time.

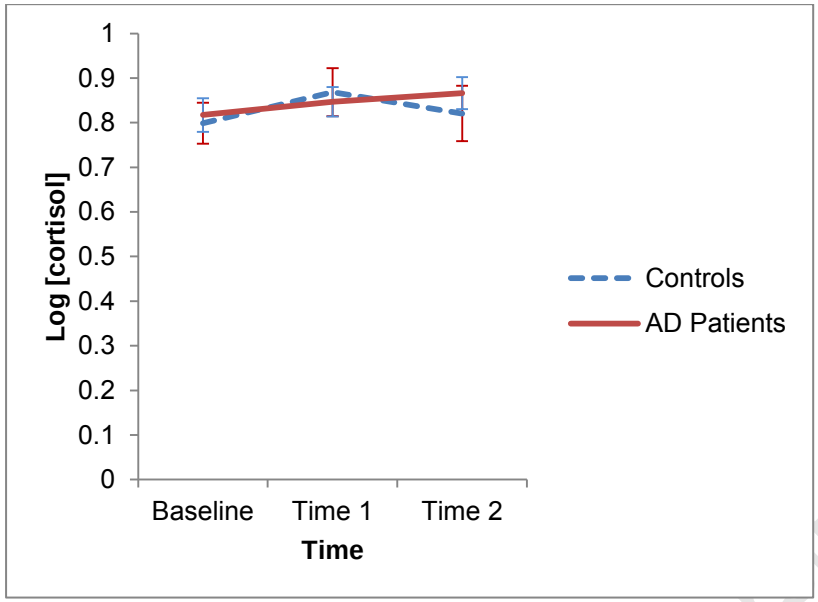
Exploratory Analyses

Changes in cortisol levels over time. Figure 13, panel (a) shows the mean log transformed cortisol levels for healthy controls and AD patients who provided salivary cortisol samples at Baseline, Time 1, or Time 2. Figure 13, panel (b) shows the mean log transformed cortisol levels for healthy controls and AD patients who provided salivary cortisol samples at Baseline, Time 1, and Time 2. In other words, panel (a) includes data for all participants who provided at least one set of samples; some did not have data for all three measurement points. This may be reflected by the slight decrease in cortisol levels at Time 2 in the controls.

In contrast, panel (b) includes data for only those participants who had complete cortisol data for all three measurement points. Therefore, this graph provides a more accurate indication of the trajectory of salivary cortisol levels over time. In both groups, panel (b) shows a small initial increase in cortisol from Baseline to Time 1 with a subsequent plateau at Time 2. The Baseline cortisol levels shown in panel (b) are lower than the Baseline cortisol levels in panel (a).

A GLM-RM examined the data depicted in Figure 13, panel (b). The GLM-RM detected no significant main effect of group, $F(1, 26) = .31$, $p = .58$, $\eta_p^2 = .01$, or age, $F(1, 26) = .15$, $p = .70$, $\eta_p^2 = .006$. The analysis did not detect a time x group interaction, $F(2, 26) = .02$, $p = .95$, $\eta_p^2 = .001$, or a time x age interaction, $F(1, 26) = .11$, $p = .83$, $\eta_p^2 = .004$.

(a)



(b)

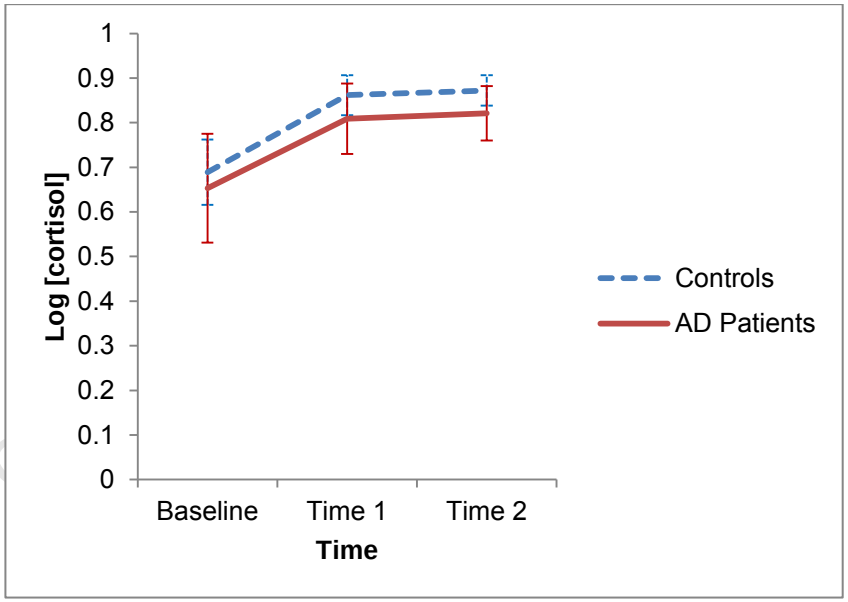


Figure 13. Panel (a) shows mean log transformed cortisol levels, with standard error bars, for participants who provided salivary cortisol samples at Baseline (n_{HC} = 66, n_{AD} = 51), at Time 1 (n_{HC} = 36, n_{AD} = 23), or at Time 2 (n_{HC} = 25, n_{AD} = 12). Panel (b) shows mean log transformed cortisol levels, with standard error bars, for only those participants who provided salivary cortisol samples at all three measurement points; (n_{HC} = 20, n_{AD} = 9).

Summary of Results

This longitudinal study investigated cognitive change and cognitive decline across a continuum of cognitive functioning, i.e. in participants who were cognitively healthy at Baseline measurement and patients with AD, over a period of 3 years. The main aim of this longitudinal study was to investigate cognitive change and cognitive decline over a period of 3 years across a continuum of cognition in participants who were cognitively healthy at Baseline measurement and patients with AD.

The particular factors of interest in this study were Baseline psychosocial (self-perceived) stress and physiological stress (cortisol), as well as APOE-ϵ4 carrier status. I also explored the predictive value of age and education for determining cognitive change and decline in this sample of older South African adults, given that both of those variables were established by the Study 1 data analyses as factors associated with cognitive function in the initial sample.

The main finding from this longitudinal study was that Baseline psychosocial stress, Baseline cortisol levels, and APOE-ϵ4 were not significant predictors of cognitive change or cognitive decline. Age, education, and group status contributed significantly to cognitive change but not to cognitive decline.

In the following section I shall first briefly summarize the sample characteristics from the Time 1 and Time 2 follow-up assessments. Then I shall summarize the findings for each hypothesis. Lastly, I will summarize the result from the exploratory analysis. As with Study 1, the purpose of this section is merely to provide an overview of the main findings from this longitudinal study. I shall interpret and discuss these results in the *General Discussion*, together with the findings from Study 1.

Sample Characteristics for Time 1 and Time 2

Participants were followed up from Baseline to Time 1 and Time 2. At Baseline there were 134 participants (n_{HC} = 69, n_{AD} = 65). At Time 1 there were 95 participants (n_{HC} = 52, n_{AD} = 43). At this time point, the AD patients were still older, had fewer years of education, and a lower level of income than the controls. At Time 2 there were 46 participants (n_{HC} = 27, n_{AD} = 19), the groups were similar in terms of age, but AD patients still had significantly fewer years of education and a lower level of income.

The number of participants decreased from Baseline to Time 1 and from Time 1 to Time 2. The reasons for this attrition will be discussed in more detail in the *General Discussion*. In general, across the three measurement points, the AD patients were older, had fewer years of education, and a lower household income. AD patients also had consistently lower cognitive scores than controls, as could be expected.

Hypothesis-Driven Analyses

Hypothesis 1 was not confirmed: Baseline levels of psychosocial stress and cortisol did not predict cognitive change. Cognitive change was measured by the change in CAMCOG-R total scores across the three measurement points, namely, Baseline, Time 1, and Time 2. Across the entire sample, change in cognitive performance, as measured by the CAMCOG-R total score, was not significantly different across these measurement points.

A GLM-RM explored whether Baseline age (in years), education (in years), APOE-ϵ4 carrier status (as a dichotomous variable, i.e. with or without), cortisol (log transformed data), psychosocial stress (as measured by PSS scores), and group status (healthy control versus AD patient) predicted cognitive change. This model indicated that age, education, and group status contributed significantly to cognitive change: older participants with fewer years of education and with AD were more likely to demonstrate cognitive change than younger participants with more years of education and no cognitive impairment. There was also a significant time x group interaction; AD patients had greater cognitive change than controls. No significant main effect of APOE-ϵ4 carrier status, cortisol levels or PSS scores was found and there were no other significant two-way interactions.

Baseline levels of psychosocial stress as measured by the PSS were not significant predictors of cognitive change. Similarly, Baseline levels of log transformed cortisol as measured by the average of two morning measurements did not predict cognitive change. When analysed over the three time points, cortisol levels were not found to change significantly from one time point to another, although graphic representation of these levels shows a mild increase from Baseline to Time 1, with a subsequent plateau from Time 1 to Time 2. This pattern was seen in controls and AD patients.

Hypothesis 2 was not confirmed: Baseline levels of psychosocial stress and cortisol did not predict decline. Cognitive decline was defined as a drop of 1 or more point(s) on the MMSE from Baseline to Time 1, and a drop of 2 or more points from Baseline to Time 2. Based on such decline, participants were divided into two groups: Decliners and Non-decliners. Baseline levels of psychosocial stress tended to be higher in Decliners than Non-decliners. Baseline cortisol levels were not found to be higher in Decliners than Non-decliners.

Hypothesis 3 was not confirmed: Participants who were APOE-ϵ4 carriers were not more likely to have cognitive decline than participants who were not carriers. This result was found for measurements at Baseline to Time 1 and from Baseline to Time 2.

Exploratory Analyses

Based on reports in the literature of cortisol increasing with age, levels of cortisol in this study were examined over the three year time period. Not all participants provided salivary cortisol samples for all three measurement points; some provided for only one or two measurement points. Cortisol levels were not found to change significantly with age; this was common to both the controls and AD patients.

In summary, the findings from this longitudinal study did not confirm my hypotheses. Baseline psychosocial stress, Baseline cortisol levels, and APOE-ϵ4 were not significant predictors of cognitive change or cognitive decline. Age, education, and group status contributed significantly to cognitive change but not to cognitive decline.

CHAPTER FOUR: GENERAL DISCUSSION

The primary aim of this thesis was to investigate the role of stress (and other well-established stress- and dementia-related vulnerabilities) in predicting age-related cognitive impairment and cognitive decline in older South African adults. Despite the fact that South Africans have high rates of exposure to traumatic life events and psychosocial stress (Williams et al., 2007), and that the country has a growing population of older adults, this is the first such investigation in this low- and middle-income country,

The dissertation presented two studies. The first was of a cross-sectional design (Study 1), and the second of a longitudinal design (Study 2). In both, cognition was the main outcome variable. Throughout, I treated it as a continuous variable, ranging across a healthy control group and an Alzheimer's disease group, because I wanted to capture a spectrum of cognitive functioning in healthy adults and in patients with mild to moderate AD.

The purpose of Study 1 was to explore, in a sample of cognitively healthy older adults and AD patients, associations between cognitive functioning, and factors established in previously published literature as being stress- and dementia-related vulnerabilities. These factors included self-perceived psychosocial stress, levels of circulating cortisol, APOE-ε4 carrier status, plasma beta-amyloid concentrations, and hippocampal volume. I explored bi- and multivariate relationships among these variables, as well as their predictive role in cognitive functioning. The investigation also included sociodemographic (e.g., age, sex, and level of complete education) and personality (e.g., resilience) variables.

A major reason driving the inclusion of so many variables of interest, and of pursuing such a wide-ranging investigation, is that there is no single factor that, in isolation, causes age-related cognitive decline and/or sporadic AD. Hence, it made sense to examine several factors simultaneously, in one large model. Using hierarchical regression analyses, I was able to identify those factors most strongly related to cognitive functioning in this sample.

Study 2 built on the results of Study 1; variables that significantly predicted cognitive functioning in Study 1 were explored as potential predictors of longitudinal cognitive change and cognitive decline in Study 2. In the latter, I assessed participants'

cognition annually over 3 years (the Baseline measurement taken in Study 1, and then two follow-ups). Study 2 also had a particular interest in investigating the role of psychosocial and physiological stress in cognitive change/decline over time.

Given the primary aims and the design elements described above, the main set of results discussed here are those from Study 1's hierarchical regression model – the largest model examined in this research (i.e., the one that included the biggest set of predictors). Discussion of these regression results is combined with the results from Study 2 pertaining to predictors of longitudinal cognitive change and decline.

The rest of this *General Discussion* is divided into several discrete sections. The first is a brief review of the sample characteristics. Then, I discuss each factor of interest in order of its entry into the regression model in Study 1 (i.e., age, sex, education, APOE-ϵ4, cortisol, and psychosocial stress). That discussion focuses on each factor in terms of its role in both the cross-sectional and longitudinal studies (that is to say, its impact on cognitive functioning at Baseline and on subsequent cognitive change and decline), and in terms of its association with stress. I then discuss resilience, Aβ, and hippocampal volumes separately because they were not included in the hierarchical regression model. Resilience was not included in the model due to its correlation with psychosocial stress, and only a subset of participants was included for the Aβ and neuroimaging components of the study. This *General Discussion* section concludes with brief considerations of the management of stress, contextual factors, methodological limitations, reflections, future recommendations, and a summary and conclusion.

Cross-Sectional and Longitudinal Results in the Context of the Literature

Sample characteristics. At baseline, the sample comprised 134 older adults, of whom 69 were cognitively healthy controls and 65 were patients with possible or probable AD, diagnosed according to the NINCDS/ADRDA and the DSM-IV-TR criteria. On average, controls were younger than AD patients and had significantly more years of education. In both groups there was almost double the number of female than male participants, although this difference was not significant in either group. Regarding SES status, AD patients had a lower socioeconomic status in terms of monthly household income than controls.

This sample was followed up over a period of up to 3 years. A number of participants were lost to follow-up, however. This attrition occurred because some (a) were no longer willing to participate, (b) were no longer testable because of ailing health, or (c) had died. Another reason for the decline in sample size from Baseline to subsequent assessments was that several people were enrolled in the study in the final year of recruitment and therefore had not been in the study long enough to have a follow-up assessment. The reason for enrolling these participants even though they would be ineligible for follow-up assessment was that I wanted to have the largest possible sample size at baseline so as to be able to include a substantial number of predictors in the regression model.

Across the entire sample, the only significant difference between the participants who remained in the study relative to those who withdrew was age; younger participants were more likely to remain in the study than older participants. Five participants died during the study; two were controls and three were AD patients. There did not appear to be any particular pattern of cognitive or functional indicators that characterized these participants.

Models of cognitive functioning at Baseline and over time. This next section will discuss the findings in relation to each main factor of interest. These factors will be discussed in order of their entry into the regression model, followed by the remaining factors that were explored outside the regression model. In other words, the factors will be discussed in this order: age, sex, level of education, APOE-ϵ4, cortisol, and psychosocial stress. I shall then discuss the results pertaining to resilience, Aβ, and hippocampal volumes.

Predictor 1: Age. This was the first predictor variable entered into the cross-sectional hierarchical regression model, and it proved to be a significant predictor of cognitive functioning. This result is not surprising because (a) numerous previous studies have established that cognitive functioning is vulnerable to the effects of ageing (Gunstad et al., 2006; Greenwood, 2000), and (b) even cognitively healthy older adults perform more poorly than young adults on cognitive tests (Gunstad et al., 2006; Tsang & Shaner, 1998; Verhaeghen & Cerella, 2002; Ferstl, 2006; Mata, Schooler, & Rieskamp, 2007).

Over the 3-year study period, including three annual measurement points, the cognitive performance of controls remained largely consistent whereas that of AD patients declined over time. This finding was not unexpected; i.e. cognitive

performance in the healthy controls was likely to remain fairly constant but the AD patients would decline over time, given that progressive cognitive decline is a key feature of, and a diagnostic criterion for, AD (Dubois et al., 2007; McKhann et al., 1984; Morris, 2006).

Data analyses in the longitudinal study also confirmed that age was a significant predictor of cognitive change; specifically, those who were older at Baseline demonstrated more cognitive change over time. Similarly, in terms of cognitive decline, those participants who declined compared to those who did not decline tended to be older; although this result did not reach statistical significance, a small-to-moderate effect size was achieved. This finding was not unexpected because increasing age has been associated with accelerated cognitive decline (Alley et al., 2007).

In terms of the relationship between age and self-reported current psychosocial stress, in both controls and AD patients there was a negative association. This finding may seem strange in light of the fact that older adults are likely to experience several stressors later in life, especially related to, for instance, the experience of chronic health conditions or the loss of a spouse (Krause, 1999). However, a decrease in self-perceived stress with advancing age may not actually reflect fewer experiences of stress. Instead, it is more likely to reflect the way in which older adults appraise stressful situations (Boeninger, Shiraishi, Aldwin, & Spiro, 2009). Another suggestion is that the nature of stress changes as people get older; stressful events are more likely to be of a chronic than episodic nature, thus providing individuals with more time to come to terms with their problems and to use previously successful strategies in managing them (Aldwin, Sutton, & Lachman, 1996). One might also suggest that, as disease progresses in AD patients, their insight may become impaired to the point that their self-reported level of psychosocial stress might not be an accurate reflection of their actual experienced levels of psychosocial stress. This latter situation might have arisen in the current study. However, at Baseline, the AD patients in this sample were in the mild to moderate stages of AD, where insight is, generally speaking, relatively well preserved.

In summary, age was an important predictor of cognitive functioning in both the cross-sectional and longitudinal studies. Additionally, age was negatively correlated with levels of self-perceived psychosocial stress. Both these findings are consistent with previously published studies.

Predictor 2: Sex. This dichotomous variable was the second predictor entered into the cross-sectional hierarchical regression model. At Baseline and across the entire

sample, there were no significant sex differences in CAMCOG-R performance; similarly, in the regression model, sex was not a significant predictor of cognitive functioning. This finding is inconsistent with previous reports demonstrating that cognitively healthy men and women perform differently on cognitive tasks (Meinz & Salthouse, 1998; Reilly, 2012; Torres et al., 2006; Voyer, Voyer, & Bryden, 1995). Most studies reporting differences in cognitive function between men and women have investigated different domains of cognitive function; i.e. women have been found to perform more strongly than men on verbal tasks and men outperform women on visuospatial tasks (Weiss et al., 2003). In my study I examined men's and women's cognitive performance on a general measure of cognitive functioning and not on specific cognitive domains. Therefore the ability to detect sex differences in cognition may have been lost because all the cognitive domains were explored together.

There was a significant association between sex and self-reported current psychosocial stress in both the AD patient and control groups. Specifically, male AD patients had significantly higher levels of psychosocial stress than female AD patients. A possible explanation for this pattern of data may relate to sex differences in stress appraisal and coping mechanisms in the context of chronic illness; biological sex plays a role in the determinants and consequences of poor health (Vlassoff, 2007). To my knowledge, levels of psychosocial stress between male and female AD patients have not been reported. I would propose that the male AD patients, in the early-to-moderate disease stage that they were in and thus with relatively preserved insight, had higher levels of psychosocial stress because they felt that their disease threatened their role as a "provider". Related to this, they may also have had financial concerns.

In the control group, females had higher levels of psychosocial stress than males. This result is consistent with reports from other studies of cognitively healthy older adults (Cohen & Janicki-Deverts, 2012). It is likely that environmental factors are likely to account for this difference. Healthy older females may be caregivers to sick family members or a spouse. They may also have concerns related to performing domestic work and maintaining a household even though they themselves are getting older and may have their own health concerns. Many of the female control participants in my study still lived independently and were responsible for many household chores, in addition to caring for a sick husband or looking after their grandchildren during the day.

There were no sex differences across the sample or within each group separately, on any of the other measures of stress (viz., lifetime traumatic experiences or morning cortisol levels). Regarding cortisol, the non-significant difference between males and females contradicts what has been reported elsewhere for older adults. For instance, Kudielka et al. (1998) showed that elderly men have higher free salivary cortisol levels than elderly women. Most studies of sex differences in salivary cortisol levels have been performed in relation to HPA axis reactivity. My study examined sex differences in unstimulated salivary cortisol levels. This methodological difference may account for the lack of a difference between male and female cortisol levels in my study.

In summary, findings from the cross-sectional study suggested that sex was not a significant predictor of cognitive functioning, but that there were sex differences in terms of self-reported psychosocial stress, and that the pattern of these differences was different in AD patients to that in controls. This difference may be accounted for by sex differences in stress appraisal and coping mechanisms between healthy older adults and older adults with chronic disease. I did not examine the predictive value of sex in the longitudinal study because (a) it was not part of any of my specific hypotheses, and (b) in this sample, it was not a significant predictor of cognitive functioning at Baseline.

Predictor 3: Level of education. This was the third predictor variable entered into the cross-sectional hierarchical regression model, and it proved to be a significant predictor of cognitive functioning. This finding supported the significant bivariate correlation between education and cognition in this sample (regardless of group status, participants with more years of education had higher cognitive scores). In fact, in the regression model, years of completed education contributed the largest amount of variance to the outcome. This finding is consistent with those reported in numerous studies describing strong associations between education and cognitive performance in older adults (Ganguli et al., 2010; Muniz-Terrera, Matthews, Dening, Huppert, & Brayne, 2009; Schneider et al., 2012).

In the longitudinal study, education also contributed significantly to the variance in cognitive change. Specifically, participants with higher levels of education scored better on the CAMCOG-R across time than participants with lower levels of education.

In contrast to the significant role of education in predicting cognitive change across the three measurement points, it was not a significant factor in predicting cognitive decline between Baseline and Time 1, and between Baseline and Time 2. In

other words, there was no difference in years of education between those who did and those who did not decline between those time points. One way to account for this apparent discrepancy is that, across time, there was more attrition of participants with low education; these individuals, therefore, were not present at Time 1 and Time 2 (see Table 20), and hence there was less variation in education in the cognitive decline models. Furthermore, the effect sizes for these analyses were small, suggesting that the sample was not large enough to detect a significant effect.

Nonetheless, this pattern of findings is consistent with previous reports showing that education level is highly correlated with cognitive performance at Baseline but is not associated with cognitive decline after that (Muniz-Terrera et al., 2009; Schneider et al., 2012; Wilson et al., 2009). Higher Baseline cognitive performance of individuals with more education might account for the lower rates of cognitive decline in those individuals. This may be as a result of education masking the effects of such decline.

As noted earlier, at Baseline measurement, controls had significantly higher levels of education than AD patients. This between-group difference remained at Time 1 and Time 2. This finding is consistent with the cognitive reserve hypothesis (Stern, 2009), which proposes that education is a proxy for a 'reserve' (associated with more flexibility and efficiency in handling adaptive problems) that protects against the clinical manifestation of neuropathology. The current finding also corresponds with those presented by Roe et al. (2007), who reported that a diagnosis of AD was less likely to be found in older adults with higher levels of education. However, this beneficial effect of education seems not to be consistent across time as education has been shown not to be a significant predictor of cognitive decline (Wilson et al., 2009; Woodard et al., 2010).

I also examined the association between level of education and (a) resilience and (b) self-reported current psychosocial stress. Across the entire sample, there was a significant correlation between education and resilience. This finding is consistent with previous studies suggesting that higher levels of education are associated with increased resilience and better coping mechanisms (Frankenberg et al., 2013). Individuals with more years of education may have developed better coping mechanisms and may have more access to resources that help them to deal with problems. For example, they may have an enhanced sense of control over their life which is likely to act as a psychological buffer against potential stressors (Fast, Gruenfeld, Sivanathan, & Galinsky, 2009).

In this sample, there was a trend for participants with higher levels of education to have lower psychosocial stress scores. This finding is consistent with previous reports suggesting that better-educated adults, partly as a result of higher SES status, have lower stress levels (Baum, Garofalo, & Yali, 1999; Grzywacz et al., 2004). This pattern of data could also be considered in light of the cognitive reserve hypothesis. For instance, if individuals with higher levels of education are better equipped to cope with pathological brain changes than individuals with lower levels of education (Meng & D'Arcy, 2012), they may also be more able and better prepared to cope with psychosocial stress. This may be because they have developed enhanced problem-solving skills and reasoning ability, for instance, and therefore may be better equipped to deal with problems that may arise. Higher levels of education are also likely to lead to improved occupational attainment and an increased level of income; these factors may ameliorate the negative effects of stress by preventing certain stressors from occurring, such as those related to severe financial stress due to a low level of occupation, or living in a less advantaged area where levels of crime are high.

In summary, findings from the cross-sectional study suggest that level of education was a strong predictor of cognitive performance. In the longitudinal study, however, education was not associated with cognitive decline. It is possible that the effect of education on cognitive decline might have been masked because several participants with lower levels of education were lost to follow-up. The general trend for education not to be a contributor to cognitive decline, however, has been reported in studies elsewhere. Finally, in a finding that was consistent with previously published studies, there was a negative correlation between years of completed education and self-reported current psychosocial stress.

Predictor 4: APOE-ϵ4. This was the fourth predictor variable entered into the cross-sectional hierarchical regression model. In this sample that was representative of the heterogeneous population of the Western Cape, the overall APOE-ϵ4 allelic frequency was 26%, and was significantly higher in AD patients (35%) than in controls (19%). This patient:control ratio is consistent with findings from other research studies, mostly conducted using European and North American populations (Farrer et al., 1997; Hua et al., 2008; Raygani et al., 2005; Tsai et al., 1994).

The allelic frequency of APOE-ϵ4 is known to be higher in African populations, generally, and in sub-Saharan Africa, particularly. In fact, the Khoi-San population of southern Africa has the highest reported ϵ4 allelic frequency in the world, at 37%

(Sandholzer, et al., 1995). Joska et al. (2010) reported an ϵ4 allelic frequency of 30% in a predominantly black African Xhosa-speaking population from the Western Cape region of South Africa.

The APOE-ϵ4 allelic frequency found for cognitively healthy controls in this study (19%) is higher than that reported in North American and European studies (Farrer et al., 1997; Sando et al., 2008b; Singh, Singh, & Mastana, 2006), but is similar to that reported in other studies of African populations. In Americans of European ancestry, the population allelic frequency is estimated at 10-12% (Farrer et al., 1997).

In contrast, the APOE-ϵ4 allelic frequency found for AD patients in this study (35%) is similar to that reported for samples of European and North American ancestry. The latter has been estimated at 40% (Mayeux, 2003; Sando et al., 2008b; Tsai et al., 1994), but it is markedly higher than frequencies reported in AD patients of African descent from West African studies (Gureje et al., 2006; Osuntokun et al., 1995).

How, then, can these results be explained? The population of the Western Cape region of South Africa is heterogeneous. This diversity arises from the establishment of a people of mixed ancestry that today is known as the South African Coloured population. Today, that group is estimated to comprise about 54% of the population of the Western Cape Province (Adhikari, 2005; de Wit et al., 2010). Most people classified as Coloured under the previous system of "race" classification have a mixed genetic ancestry, with significant contributions from the indigenous African populations as well as from the European settler populations. Recently, a genome-wide analysis of the structure of the Coloured population in the Western Cape was performed. This analysis revealed that the major ancestral components of this population comprised mainly Khoi-San, Bantu-speaking Africans, European, and a smaller Asian contribution (de Wit et al., 2010). Because 55% (25 controls and 49 AD patients) of the participants in the current sample self-identified as Coloured, the high background allelic frequency of ϵ4 in the sample might be explained by this indigenous ancestry.

From an evolutionary perspective, the ϵ4 allele of the APOE gene has been considered a 'thrifty' allele (Corbo & Scacchi, 1999). This means it has an evolutionary advantage in conditions of nutrient deprivation and starvation. It may also be protective against infectious diseases (Wozniak et al., 2002), and it may protect cognition in children in LAMIC rural areas where the burden of enteric disease is high (Oria et al., 2005). However, the allele appears to become disadvantageous when the human lifespan increases, and when the same population it protected under challenging

conditions, is exposed to an industrialized "Western" environment where relatively cheap, processed, low-fibre and high saturated fat foods are available more readily. Hence, the allele that was once protective becomes a risk factor for certain medical conditions, including AD (Corbo & Scacchi, 1999). The data presented here support this argument: the AD patients had a significantly higher APOE-ϵ4 frequency than controls.

The ϵ4 allele, already present in a higher frequency in our study population, may increase susceptibility to developing AD in this ageing, urbanised population. Indeed, this phenomenon has been reported for other industrialized countries. Other African studies, including one comparing a Yoruba population in Nigeria with that of a genetically related African-American population in Indianapolis, USA, did not find an association between presence of APOE-ϵ4 and AD in the Nigerian population (Gureje et al., 2006; Osuntokun et al., 1995), but such an association was found in the African-American population (Murrell et al., 2006). The lack of association between presence of APOE-ϵ4 and AD in the Nigerian population is probably accounted for by genetic, environmental, and dietary factors, as well as genetic/environmental interactions (Hall et al., 2006). In my study, I did not explore the role of other genetic (non-APOE), environmental, or dietary factors on the relationship between APOE-ϵ4 and AD. Future research could examine whether such factors play a role in this population.

The biological mechanisms underlying the increased susceptibility to AD conferred by possession of the APOE-ϵ4 allele are not the primary focus of my study. However, mechanisms that have been postulated include a greater susceptibility of the E4 isoform of the protein, compared with the E2 and E3 variants, to oxidative damage (Lane & Farlow, 2005). The damaged or oxidised APOE-ϵ4 could then result in defective cholesterol transport to damaged CNS structures during the process of cell repair. Also, the clearing of beta-amyloid from the brain by the oxidized APOE-ϵ4 may be less efficient than that by the E2 or E3 isoforms (Mahley, Weisgraber, & Huang, 2009).

Data from the cross-sectional study suggested that APOE-ϵ4 carrier status was a significant predictor of cognitive functioning: Those with the ϵ4 allele performed more poorly on the CAMCOG-R than those without the allele. Although AD patients had a significantly higher ϵ4 allelic frequency than controls, within the AD patient group there was no significant difference, at Baseline, in cognitive performance between those patients with and without ϵ4.

Data from the longitudinal study suggested that APOE-ϵ4 carrier status was not a significant predictor of cognitive change across time. Furthermore, there was a relatively equal distribution of APOE-ϵ4 carriers and non-carriers among participants who demonstrated cognitive decline between Baseline and Time 1, or between Baseline and Time 2. The lack of an association between APOE-ϵ4 carrier status and cognitive change/decline stands in contrast to the findings of Cosentino and colleagues (2008); in their study, APOE-ϵ4 carrier status was associated with faster cognitive decline in an incident population-based AD group. Those authors proposed that the effect of APOE-ϵ4 on cognitive decline is prominent in the earliest stages of AD. APOE-ϵ4 has also been associated with cognitive decline in non-pathological ageing (Schiepers et al., 2012).

In contrast to the relationship between APOE-ϵ4 and cognitive decline in cognitively healthy adults, there are recent data to support the current findings of a lack of association between APOE-ϵ4 and cognitive decline. Bunce et al. (2013) examined APOE genotype and cognitive change in a longitudinal population-based study of cognitively healthy adults in their 20s, 40s, and 60s. They reported that without dementia-related neuropathology, the APOE genotype had no effect on cognitive change in early, middle, or late adulthood. Where they did find an ϵ4-related cognitive decline in older adults, they suggested it was linked to a preclinical period of dementia that had not yet been identified as such.

In summary, the APOE-ϵ4 allelic frequency in this sample was relatively high and can be explained by the partial African ancestry of the population from which the sample was drawn. In the current sample, APOE-ϵ4 carrier status was a significant predictor of cognitive functioning at Baseline, but not of cognitive decline over the follow-up period. Furthermore, there were no APOE-ϵ4 by cortisol interaction effects with regard to cognitive functioning. Other environmental factors not explored in this study (e.g., diet and increased longevity within the population) are likely to interact with the APOE-ϵ4 allele and increase the susceptibility to developing AD. APOE-ϵ4 was also explored in relation to psychosocial stress and cortisol; these findings are discussed in the relevant sections below.

Predictor 5: Cortisol. The log transformed salivary cortisol data constituted the fifth predictor variable entered into the cross-sectional hierarchical regression model. As noted earlier, a major driving component of the research described in this dissertation is the concept that stress is linked to cognitive impairment via changes that

occur in HPA-axis functioning. A marker of HPA-axis activity is the hormone cortisol (Aguilera, 2011; Foley & Kirschbaum, 2010; Henry, 1992; McEwen & Sapolsky, 1995; McEwen & Stellar, 1993; Sapolsky, 1996; Selye, 1976; Tsigos & Chrousos, 2002). There is strong evidence that chronically elevated cortisol levels can cause damage to the brain and contribute to age-associated pathology such as neurodegeneration (Aguilera, 2011; McEwen & Stellar, 1993; Sapolsky, 1999).

Several studies have explored the association between chronically elevated cortisol levels and cognitive functioning in ageing. In my cross-sectional study, morning salivary levels of circulating cortisol did not predict cognitive functioning. This lack of association was found in controls, in AD patients, and when analysed across the entire sample; it was true in bivariate correlational analyses and in the regression model. This set of findings disconfirmed my initial hypotheses, and stands in contrast to some previous studies (see Lee et al., 2007; Lupien at al., 1994). A possible reason for this discrepancy may relate to the cortisol measurements themselves, i.e. the time of day and the number of measurements obtained. In the studies mentioned above, several cortisol measurements were obtained throughout the day. In my study, I obtained one 9am measurement of cortisol per day for two consecutive days at each time point. It is possible that obtaining several measurements of cortisol may have produced a different result. However, another study using the 9am salivary cortisol measurement reported an inverse association between cortisol and memory recall in older adults with mild cognitive impairment but this association was not found in controls or AD patients (Wolf, Convit, Thorn, & de Leon, 2002). One could also speculate about the role of the inverted U-shaped function in regard to why I did not find an association between cognition and cortisol (Diamond, Bennett, Fleshner, & Rose, 1992). This inverted U-shape relationship implies that very high or very low levels of cortisol impair cognition, while moderate levels may facilitate memory (Lupien & McEwen, 1997). The association between cognition and cortisol levels reported by Lupien et al. (1994) was for high cortisol levels. The cortisol levels of participants in this study may not have been high enough to impair cognition. However, this is rank speculation because I did not have a measure of the AD patients' pre-morbid basal cortisol levels against which to compare their current levels and thus based on these data I cannot provide support for a U-shaped relationship.

However, it could also be argued that an association between morning salivary cortisol levels and cognitive functioning just does not exist. For example, Peavy et al.

(2007) found a lack of association between cortisol levels and performance on memory tests. Additionally, Schrijvers et al. (2011) reported that morning serum levels of cortisol were not related to cognitive functioning in the Rotterdam study, a large prospective population based cohort study. One might question the fact that the Rotterdam study used serum and not salivary cortisol, as in mine and the study of Peavy et al. However, studies that have used serum cortisol as opposed to salivary cortisol are comparable because serum and salivary cortisol are well correlated and salivary cortisol levels have been shown to be a surrogate for serum cortisol (Dorn, Lucke, Loucks, & Berga, 2007).

In the cross-sectional study, the lack of a significant between-group difference for controls and AD patients in terms of morning levels of salivary cortisol was unexpected. In my *a priori* hypothesis I predicted that cortisol levels would be higher in AD patients than in controls. The association between AD and cortisol levels has been reported elsewhere (Csernansky et al., 2006; Giubilei et al., 2001). Cortisol levels in AD patients have been shown to be higher compared to cognitively healthy controls (Umegaki et al., 2000; Swanwick et al., 1998). One way to account for the non-significant between-group difference in my study may relate to a flattening of the HPA axis diurnal amplitude. HPA-axis activity is known to flatten with age, and particularly in older adults with dementia (Ferrari et al., 2000; Deuschle, 1997). The AD patients in my study were older than the controls; a combination of older age and disease progression may have produced a flattened HPA-axis profile in the AD patients, thus possibly explaining similar cortisol levels between the groups. However, this is a tentative suggestion because I did not have knowledge of whether the AD patients' HPA axis profiles differed from controls at Baseline.

Findings from the longitudinal study showed a small but statistically non-significant increase from Baseline in morning levels of circulating cortisol over the 3-year follow-up period in both controls and AD patients. Baseline cortisol levels had no predictive effect on either cognitive change or cognitive decline over time. These data are not consistent with the glucocorticoid hypothesis of the pathophysiology of mild to moderate AD. A lack of support for this hypothesis does, however, confirm similar previous reports (Schrijvers et al., 2011; Swanwick et al., 1998). In the study by Swanwick et al., they reported that, although HPA-axis dysfunction correlated with severity of AD at Baseline, it did not increase at follow-up. A possible reason for this finding in my study relates to evidence which suggests that the effects of elevated

cortisol are only noticeable when those levels are sustained over an extended period of time (Lupien et al., 1998). In this sample, controls and AD patients reported similar levels of lifetime stress. Therefore, it could be speculated that if there were no between-group differences for lifetime stress then there may not have been between-group differences in levels of cortisol. However, the relationship between the experience of psychosocial stress and the release of cortisol and its circulating levels is not straightforward. For example, chronic stress may evoke adaptive physiological mechanisms so that cortisol levels may not increase proportionately to stress levels (de Kloet, Joels, & Holsboer, 2005). Another possible explanation for the lack of significant change in cortisol over time relates to reports of high intra-individual stability of salivary cortisol (Shirtcliff et al., 2012). Researchers in this field have hypothesized that cortisol may be regarded as a psychological trait which may account for its stability over time (Wust, Federenko, Hellhammer, & Kirschbaum, 2000). Furthermore, cortisol and individual vulnerability to the negative effects of stress on cognitive functioning may thus be influenced to some degree by genetic factors (Kreek, Nielsen, Butelman, & LaForge, 2005; Polk, Cohen, Doyle, Skoner, & Kirschbaum, 2005; van Santen et al., 2011; Wust, et al., 2000).

One such genetic factor that has been associated with stress and with AD is APOE-ϵ4. Study 1's data analysis detected no significant main effect of either cortisol or APOE-ϵ4, and no significant interaction effect of the two variables, on cognitive functioning. These findings, then, are not consistent with reports in previous studies suggesting that the interaction between higher stress levels and presence of APOE-ϵ4 is associated with poorer cognitive functioning (Gerritsen, Comijs, Deeg, Penninx, & Geerlings, 2011; Lee et al., 2008; Peavy et al., 2007). Possible reasons for the discrepancy may relate to the measurement of cortisol. For instance, Lee and colleagues (2008) measured salivary cortisol at the time of cognitive testing, therefore measuring HPA-axis reactivity to the assessment situation. However, in my study I measured unstimulated morning cortisol levels and did not measure HPA-axis reactivity. The APOE-ϵ4 by cortisol interaction may be stronger when HPA axis reactivity rather than unstimulated cortisol levels is measured. Hence, Lee et al. may have shown a stronger association of cortisol and APOE-ϵ4 with cognition because they measured the actual response to stress and the sensitivity of the HPA axis feedback system.

Another reason for the lack of an APOE-ϵ4 by cortisol interaction may relate to the measures of cognition employed in various studies. Those studies that have found

significant APOE-ϵ4 by cortisol interaction effects have used discrete measures of memory. In my study, however, I used a measure of general cognitive functioning and did not have a discrete measure of memory. One might suggest that using a specific measure of memory might have produced a different result, given that cortisol affects the hippocampus which plays a crucial role in new learning and memory. Thus, larger differences in memory performance than in general cognitive performance may have demonstrated a significant APOE-ϵ4 by cortisol interaction. On the other hand, though, one could argue that this effect should still have been seen in my study because glucocorticoid receptors are distributed throughout the brain and thus several domains of cognition may be affected by such an interaction, as shown by Lee et al. (2008).

The discussion above has focused on the factors of interest in this study and their association with cortisol. There are, however, several other factors known to be associated with salivary cortisol levels, such as age and BMI (Daniel et al., 2006), mood (Het, Schoofs, Rohleder, & Wolf, 2012; Polk, Cohen, Doyle, Skoner, & Kirschbaum, 2005), activity level (West, Otte, Geher, Johnson, & Mohr, 2004; Rimmele et al., 2009), and medical conditions (Roberts, Wessely, Chalder, Papadopoulos, & Cleare, 2004). Hence, even though there were no between-group differences in terms of BMI in my study, and age was controlled for, it is possible that other factors contributed to the lack of association between salivary cortisol levels and cognition. Furthermore, it must be noted that I only measured morning salivary cortisol levels which do not reflect the circadian rhythm of cortisol secretion. Future studies may benefit from including several measurements of cortisol throughout the day to obtain an indicator of the HPA axis functioning.

In summary, in the current sample there was no significant association between cortisol and cognitive functioning at Baseline, or between cortisol and cognitive change/decline over time. This finding, while inconsistent with some studies, has been reported in other studies. There are several possible reasons for this lack of association which may relate to the measurement of cortisol itself (i.e. the time of day and the number of measurements), measurement of unstimulated cortisol, flattening of the HPA axis diurnal amplitude in the AD patients, or the possibility, as demonstrated in this sample and in other studies, that morning levels of cortisol are not predictors of cognitive functioning or decline.

Predictor 6: Psychosocial stress. This was the sixth, and final, predictor variable entered into the cross-sectional hierarchical regression model. It proved to be a non-significant predictor of cognitive functioning.

Regarding measurement of 'psychosocial stress', in this study scores on the Perceived Stress Scale (PSS) captured the construct. In other words, these scores provided an indicator of how stressful participants perceived their lives to have been over the past month. This self-perceived psychosocial stress resulted primarily from the experience of minor daily stressors and agitations. One might question, then, whether AD patients were reliably able to report experiencing such stress, given their memory impairment. These patients were, however, in the mild to moderate stages of AD and were capable of recalling how stressful their life had felt over the past month. In several cases, relatives of the patients confirmed that the answers provided by the patients were veridical, to the best of their knowledge.

In the current sample, AD patients had significantly higher levels of Baseline psychosocial stress than controls. Clearly, one can make no inferences of causation based on this limited dataset and design. One possible interpretation of the data, however, is that AD patients may have had higher levels of psychosocial stress throughout their lifetimes, and this may have contributed to their development of the disease. This interpretation is supported by longitudinal studies that have tracked psychosocial stress and risk of developing AD over several years (Johansson et al., 2010; Wilson et al., 2003; Wilson, Begeny, Boyle, Schneider, & Bennett, 2011). For example, in a 35 year longitudinal study, Johansson et al. (2010) examined mid-life stress and the risk of dementia (105 of the 161 dementia cases were AD). Reports of frequent/constant stress at one, two, or three time points during this period were related to risk of developing dementia, including AD. This interpretation is also supported by reviews which implicate stress as a role player in the development of AD (Lupien, McEwen, Gunnar, & Heim, 2009; Sotiropoulos et al., 2008).

An alternative interpretation is that the AD patients may have reported higher levels of psychosocial stress because their memory (and other cognitive) problems concerned them greatly. This interpretation is supported by findings that AD patients experience and demonstrate high levels of anxiety (Ferretti, McCurry, Logsdon, Gibbons, & Teri, 2001; Porter et al., 2003; Teri et al., 1999). Furthermore, recent studies have found that AD patients report lower levels of quality of life compared with reports from caregivers. AD patients with the lowest ratings of quality of life had a

better cognitive status and more depression (Conde-Sala et al., 2013; Xing et al., 2012). The latter is known to be associated with stress (Sotiropoulos et al., 2008).

A third interpretation is that higher levels of psychosocial stress in AD patients might be attributable to their lower SES status levels (recall that, in this sample, AD patients reported having a significantly lower monthly household income than controls). Cohen and Janicki-Deverts (2012) studied the distributions of psychological stress in the United States in a series of probability samples. They found that adults with low SES status were most likely to experience the highest levels of stress and associated disease risk. However, given that those findings (and those reported here) are strictly correlational, one should be cautious in suggesting that increased financial concerns have a significant causal impact on self-reported levels of psychosocial stress, and that this chain then represents a risk for AD.

Of course, the three interpretations outlined above might not (and probably do not) exist in isolation from one another. In other words, accepting one interpretation does not mean one has to discard the other two. Rather, it is possible that all three (and, perhaps, other factors) contribute in some degree to the observed relationship between SES status and psychosocial stress in AD patients. Distinguishing the precise mechanisms underlying the relationship is, clearly, a complex task, and one that was not the focus of this investigation. Here, it must suffice to say that, in the current sample, AD patients reported experiencing more psychosocial stress and lower income than controls. Psychosocial stress did not play a significant role in predicting cognitive functioning in the sample. SES status was not specifically explored with psychosocial stress because SES status was highly correlated with education. Rather, education and psychosocial stress relationships were examined and those have already been discussed.

As mentioned earlier, psychosocial stress was not a predictor of cognitive functioning. Of note, however, is that this lack of association between psychosocial stress and cognitive functioning is not consistent with some previous reports. For example, Neupert and colleagues (2006) found, in a sample of 333 older adults in the VA Normative Aging Study, that daily stressors were associated with everyday memory failures. Similarly, research involving a cohort of older men from the Normative Aging Study found similar associations between psychosocial stress (as measured by the PSS) and MMSE score (Peters et al., 2010). The authors reported that participants with higher PSS scores had a 0.57-point lower MMSE score.

Results from the longitudinal study suggested that Baseline levels of psychosocial stress did not have any effect on cognitive change over time. Again, this finding stands in contrast to results reported by Wilson et al. (2007), who found, in a sample of 1, 256 cognitively healthy individuals (mean age: 76.8 years) that individuals who were more prone to experience psychological distress experienced more cognitive change over a 12-year period.

In terms of cognitive decline, there was no significant difference in Baseline levels of psychosocial stress between those participants who declined and those who did not. My finding does not correspond with those from epidemiological studies that have demonstrated that cognitive decline is accelerated by chronic psychological stress (Peavy et al., 2009; Wilson et al., 2007).

A possible explanation for the discrepancy between the current findings and those of Peavy et al. (2009) and Wilson et al. (2007) relates to the stage of cognitive functioning that participants were in. Peavy et al. only found an association between stress and cognitive decline in participants who were already cognitively impaired, while Wilson and colleagues only examined stress and worsening cognitive function in healthy adults. It is possible that the effects of stress differ depending on the level of cognitive functioning or stage of cognitive decline at which one is. The differential effects of stage may have been lost if all participants were regarded as one category. However, in my study, post-hoc analyses indicated a similar non-significant finding between cognitive decline and psychosocial stress when examined in the control and AD patient groups separately. A post-hoc power analysis for the entire sample showed that there was insufficient power ($N = 95$) to detect a medium-sized effect; actual power of 0.40, with ideal power ($1 - \beta$) set at .80 and $\alpha = .05$, two-tailed, and a small-to-medium effect size of 0.36.

In summary, the data analyses reported here suggest that current levels of psychosocial stress do not have a significant effect on (a) the baseline cognitive functioning of older adults, and (b) subsequent cognitive change or decline. These findings contrast with several previous studies which have found such associations. Furthermore, these findings were unexpected because South Africa has high levels of community and interpersonal violence, as well as a history of severe socio-political instability (Barber, 1999; Finchilescu & Dawes, 1999; Hamber & Lewis, 1997). Thus, it is likely that older adults who have lived in this country for all or most of their lives would have experienced numerous traumatic life events and would have relatively high

levels of psychosocial stress (Williams et al., 2007). One might expect, then, given previous literature, that a stress-cognitive function link would be clear in a South African sample.

Findings regarding resilience. Levels of resilience may account for some of the individual differences in the response to psychosocial stress and adversity. Although resilience (as measured by the CD-RISC) was not included as a predictor variable in the cross-sectional hierarchical regression model, I did conduct a subset of analyses featuring it because of its purported link to lifetime trauma and current psychosocial stress.

In controls, AD patients, and across the entire sample, there was a significant inverse relationship between levels of resilience and psychosocial stress, indicating that participants with lower levels of resilience had higher levels of psychosocial stress. This finding was expected and is consistent with similar results found elsewhere in older adults (Yehuda & Flory, 2007; Wagnild, 2003). Furthermore, across the entire sample, education and resilience were positively correlated, indicating that participants with higher levels of education had higher levels of resilience. This finding is not surprising because higher levels of education are likely to lead to a better occupation and living conditions, which in turn may provide a more supportive environment than one might have with lower levels of education and poor job prospects. However, any causal inference regarding the relationship between level of education and resilience in later life in this study cannot be drawn. Furthermore, education and income are closely intertwined, and the single effect of one variable over another on resilience cannot be determined. It is likely that both these factors affect levels of resilience, independently and interactively (Muller, 2002; Taylor, et al., 2010).

Findings regarding beta-amyloid. The literature indicates that changes in the levels of the different Aβ peptides that are produced are detectable in the plasma, occur in a preclinical stage of AD, and they persist with disease progression.

In this study, AD patients had a lower plasma Aβ1-42/Aβ1-40 ratio than age-matched controls. Although this between-group difference was not statistically significant, the comparison was associated with a relatively large effect size (d = 1.05). Current opinion in the literature suggests that a lower plasma Aβ1-42/Aβ1-40 ratio predicts the development of AD (Graff-Radford et al., 2007; Koyama et al., 2012; van Oijen, Hofman, Soares, Koudstaal, & Breteler, 2006). Furthermore, a lower plasma Aβ1-42/Aβ1-40 ratio has been observed in AD patients with established disease

compared with healthy controls (Lui et al., 2010). A recent study confirmed the decline of this ratio in AD patients over a period of 18 months (Rembach et al., 2013). The data reported here were generally consistent with this literature in that the plasma Aβ1-42/Aβ1-40 ratio in my study correlated positively and significantly with cognitive performance. No inference can be made, however, regarding the causal role of the plasma Aβ1-42/Aβ1-40 ratio in cognitive performance. It was not surprising, though, that the plasma Aβ1-42/Aβ1-40 ratio in this study was lower in AD patients compared with controls. The AD patients were in the mild to moderate stages of the disease and one could speculate that they had already experienced this decline in the Aβ1-42/Aβ1-40 ratio.

Regarding the specific concentrations of Aβ1-42 and Aβ1-40, I found lower levels of plasma Aβ1-42 and slightly higher levels of Aβ1-40 in AD patients relative to controls, but these results were not statistically significant. Previous findings with regards to the independent roles of Aβ1-42 and Aβ1-40 in AD have been contradictory: Some studies have reported elevated levels of Aβ1-42 and Aβ1-40 in the early stages of AD (Mayeux et al., 2003), whereas others reported that only Aβ1-40 was higher in AD patients than in controls (Mehta et al., 2000). Consistent with the current findings, Lui et al. (2010) reported lower plasma Aβ1-42 levels in AD patients relative to controls. Furthermore, a meta-analysis of 12 cross-sectional studies concluded that AD patients had marginally but non-significantly lower plasma Aβ1-42 levels compared with cognitively normal individuals; there was also no significant difference in Aβ1-40 levels (Song et al., 2011).

A study investigating the predictive value of Aβ in an elderly population without dementia ($N = 1, 125$) found that higher plasma Aβ1-42 levels at the onset of the study related to a threefold increased risk of AD (Schupf et al., 2008). However, a decline in Aβ1-42 and a decreased Aβ1-42/Aβ1-40 ratio was linked with conversion to AD. In my study, the AD process had already begun in the cognitively impaired AD participants and plasma Aβ1-42 may have already declined from previous levels.

Murine studies have reported relationships between psychosocial stressors, HPA-axis response to stress, elevated glucocorticoids, and increased production of Aβ (Carroll et al., 2011; Dong & Csernansky, 2009; Green et al., 2006). The direction of the relationship is a positive one, where increased stress is associated with increased Aβ production. For example, Kang et al. (2007) demonstrated that chronic and acute stress

increased Aβ levels in the brain interstitial fluid in amyloid precursor protein transgenic mice.

In this study, when analysing the entire sample, I found that there were no significant correlations between any of the Aβ levels and psychosocial stress, between Aβ1-42 and cortisol, and between Aβ1-40 and cortisol. There was, however, a significant negative correlation between cortisol levels and the Aβ1-42/Aβ1-40 ratio (i.e. lower Aβ1-42/Aβ1-40 ratios were associated with higher cortisol levels). This finding is interesting because, as noted above, lower Aβ1-42/Aβ1-40 ratios are also strongly related to the presence of AD. This set of findings raises the question about whether there might be an interactive role of stress and Aβ in humans with AD. However, all the nuances of this question make it a complex one, and it would need examination in a longitudinal design featuring a much larger sample of older adults than that reported on here. Aβ is known to change over time; future studies that monitor the trajectory of plasma Aβ levels in cognitively healthy and AD individuals are likely to yield reliable information in this regard.

To my knowledge, this is the first study to determine plasma Aβ peptide concentrations in older adults from an African population. The results from my study did not show any obvious relationships between Aβ and psychosocial stress. However, the significant negative correlation between cortisol levels and the Aβ1-42/Aβ1-40 ratio was interesting and raises questions for future research. Although previously published studies have found some associations between plasma Aβ and the presence and progression of AD, it remains an open question as to whether a plasma-based test for the detection of Aβ is going to become a useful diagnostic marker for AD. One could speculate that if well-designed longitudinal studies of plasma Aβ and risk of AD showed promising results, this could pave the way for a valid, non-invasive method in which to diagnose AD.

Findings regarding hippocampal volume. The hippocampal formation is important to research in the cognitive neuroscience of ageing, and to current research, because (a) it is one of the earliest brain structures to be affected in AD, (b) it may incur structural and functional damage as a result of stress and cortisol levels (Bremner, 2006), and (c) hippocampal damage can impair learning and memory performance (Lupien et al., 1997b). To my knowledge, this is the first African study that reports results of manual tracing of the hippocampi of older adults with and without cognitive impairment.

In this sample, AD patients had significantly smaller right, left, and total hippocampal volumes than controls. These findings are consistent with those of previously published studies (Jack, Jr. et al., 1997; Pennanen et al., 2004). Other findings were as follows: First, across the entire sample, ICV-adjusted hippocampal volumes (right, left, and total) were significantly associated with MMSE and Learning subscale scores. Second, AD patients with the ϵ4 allele had smaller ICV-adjusted total hippocampal volumes than those without the ϵ4 allele. This latter finding is consistent with those reported by several previous MRI studies (Geroldi et al., 1999; Hashimoto et al., 2001; Pievani et al., 2011; Spampinato, Rumboldt, Hosker, & Mintzer, 2011).

Review of the literature indicates evidence for the relationship between stress and hippocampal volume. In animals, a body of literature supports the notion that the hippocampus is selectively vulnerable to the effects of chronic stress (Lee, Jarome, Li, Kim, & Helmstetter, 2009; Magarinos, McEwen, Flugge, & Fuchs, 1996; McEwen & Sapolsky, 1995; Watanabe, Gould, & McEwen, 1992). Similarly, in humans, elevated cortisol levels are associated with and predictive of hippocampal atrophy (Lupien et al., 1998; Lupien et al., 2009; McEwen & Sapolsky, 1995; Sapolsky, 2000). The current data analyses did not detect such associations, however. There was no main effect of cortisol (and no cortisol by APOE-ϵ4 interaction) on ICV-adjusted hippocampal volumes. Furthermore, there was no significant association between psychosocial stress and hippocampal volume.

There remains controversy surrounding the question of whether, in humans, encounters with stressors, and consequent activation of the physiological stress response, causes reduced hippocampal volumes. A relatively large body of literature has shown that, in comparison with controls, individuals diagnosed with post-traumatic stress disorder (PTSD) have smaller hippocampal volumes (Bremner, 2005; Gurvits et al., 1996; Smith, 2005; Villarreal et al., 2002). This finding suggests that reduced hippocampal volume may result from repeated exposure to stress and a consequent increase in glucocorticoid levels. However, it is also possible that smaller hippocampal volume may predispose individuals to the development of pathological post-traumatic stress responses, such as those seen in PTSD (Sapolsky, 2002; Wignall et al., 2004; Woodward et al., 2006). The latter idea is supported, for example, by the finding that, in monozygotic twins with different trauma exposure histories, smaller hippocampi constituted a pre-existing vulnerability for the development of stress-related psychopathology (Gilbertson et al., 2002). The current state of the literature supports a

role for stress in hippocampal atrophy. This is well demonstrated in animals; evidence in humans is becoming increasingly convincing. However, regarding the human studies, there is no conclusive evidence for the direction of the relationship between stress and hippocampal atrophy.

In summary, findings from my study indicated that hippocampal volumes in AD patients were significantly smaller than in controls. This finding is in agreement with MRI studies globally. In AD patients, smaller hippocampal volumes were associated with the APOE-ϵ4 allele. Such findings suggest a role for APOE-ϵ4 in hippocampal atrophy in AD; however, the role at this point is purely one of association, as causation cannot be established. Cortisol levels were not associated with hippocampal volumes.

Results in Terms of the Research Framework

Having now discussed the results pertaining to investigation of all the variables of interest in this study (i.e., their relationships with cognitive functioning, with cognitive change, with cognitive decline, and with stress), I refer back to Figure 3 (Study 1, page 61). That figure was a schematic representation of the research areas of interest in this study, namely, age, education, resilience, psychosocial stress, cortisol, APOE-ϵ4, beta-amyloid, and hippocampal volume, and it addressed a key theme: that there are several factors associated with cognitive impairment, and that some of these factors are inherent and some are modifiable in early life but less so in later life. The methods employed in this dissertation have shown that the possible effects of these factors, on cognitive functioning and on each other, are measureable through the use of neuropsychological testing, neuroradiological imaging, and biochemical tests of blood samples.

The results presented in Study 1 and Study 2 are in keeping with the general framework of this dissertation illustrated by that figure: multiple factors are associated with cognitive functioning in older adults, and some of those factors are associated with cognitive decline post-baseline. With the interplay among different factors, the results show that there is no single profile of factors predictive of cognitive functioning or cognitive decline.

Furthermore, the figure alluded to the lasting effects that stress (psychosocial and physiological) can have on cognitive function and on brain structure. In this sample, however, stress was not a significant predictor of cognitive functioning at the

Baseline assessment or of cognitive change/decline over time. However, in participants with measured cognitive impairment (i.e., those in the AD patient group), levels of psychosocial stress were significantly higher than in controls.

The Significance of Stress in the Context of Cognition: Can it be Managed?

Even though my study did not find stress to be a significant contributor to cognitive functioning or change/decline, this result appears somewhat anomalous in the context of the broader literature. Hence, it remains an important factor for consideration especially because it is potentially modifiable. In this section, I focus briefly on the importance of stress in cognitive functioning and ways in which stress can be dealt with in order to minimise its adverse effects on cognition.

All human beings experience stress-inducing events during their lifetime. Some of these events are completely out of the individual's control, especially when they occur early in life. Human and animal studies have shown that early developmental stress, which can even occur during the intra-uterine and neonatal periods, can have long-lasting effects that influence ageing (McEwen, 2008; Solas et al., 2010).

On the other hand, even though we are perhaps unable to control the occurrence of traumatic life events and daily stressors, we might be able to control our response to stress. In other words, the physiological response to an event that might otherwise be stressful is a potentially modifiable variable among the numerous factors (sociodemographic, environmental, genetic, personality, etc.) that affect the way in which we age.

Pharmacological manipulation and psychosocial management are two ways of modifying or controlling the physiological stress response. An example of the former is the use of beta-blockers (e.g., propranolol). The experience of stressors activates, among others, the locus coeruleus-noradrenergic system. This activation results in the release of norepinephrine, a stress hormone (Berridge & Waterhouse, 2003; Charmandari, Tsigos, & Chrousos, 2005; Tsigos & Chrousos, 2002). This hormone increases the state of arousal, which precipitates further physiological changes as part of the stress response (Morilak et al., 2005). One of the roles of beta-blockers is to inhibit the action of norepinephrine (Aston-Jones, Gonzalez, & Doran, 2007; Chavey, 2000; Dodt, Breckling, Derad, Fehm, & Born, 1997).

The use of beta-blockers to inhibit the negative effects of stress on the brain has been examined in experimental studies. For example, in a sample of participants who had recently experienced a traumatic event (motor vehicle accident or physical assault), some of the participants were prescribed a non-selective beta blocker, propranolol, 2-20 hours post-trauma (Vaiva et al., 2003). The results indicated that PTSD rates were higher in participants who did not take the drug compared with those who did take it. Based on those results, the authors suggested that immediate treatment with propranolol post-trauma might have a mitigating or even preventative effect on subsequent development of PTSD. Similarly, a Cochrane Review assessed findings in 35 short-term randomised controlled trials of pharmacotherapy for PTSD (Stein, Ipser, & Seedat, 2006). The types of pharmacotherapy reviewed included several different lines of treatment, such as anti-depressive agents, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, or tricyclic drugs. The review reported that symptom severity for 17 trials was significantly reduced in the medication groups, compared to the placebo groups.

The effects of stress are also amenable to social interventions and psychotherapeutic strategies. Such non-pharmacological management of stress includes developing coping strategies, such as relaxation or social skills, to deal with anxiety- and stress-evoking experiences (Cottraux, 2002). Cognitive therapy is also effective in the management of stress (Baddeley & Gros, 2013; Granath, Ingvarsson, von, & Lundberg, 2006; Jenni & Wollersheim, 1979). Regular exercise, healthy diet, and social support have also been shown to be targets for behavioural interventions that moderate the effects of chronic stress and provide beneficial effects for brain and body health (Cohen & Wills, 1985; Duman, 2005; McEwen & Wingfield, 2010; Petruzzello, Landers, Hatfield, Kubitz, & Salazar, 1991; Scully, Kremer, Meade, Graham, & Dudgeon, 1998).

The literature provides support for the potential modification of stress. This is encouraging in light of the fact that stress has been linked to several health conditions, including mental health. Although stress, in isolation, did not have an influence on cognitive functioning in my study, it was related to other factors which may then affect cognitive functioning. Thus, finding effective ways to manage stress may have benefits on several areas of health, which in turn may then benefit cognition.

The Broader Social Perspective

As is the case in most LAMICs, South Africa will, over the next few decades, continue to experience urbanisation and an increase in life expectancy (United Nations Population Division, 2006). Age-related diseases in South Africa are going to become more prevalent because people are living longer. The South African healthcare system is currently ill-equipped to deal with the burden of age-related disease, and there are few community-based and residential care facilities for people with AD and dementia (Kalula et al., 2010). Furthermore, Baiyewu and Potocnik (2005) reported that, at their count, there were only six outpatient psychiatric facilities for older adults in South Africa. This scarcity of such resources is not unusual in the African context or in LAMICs in general, and the responsibility of caring for older adults falls on relatives (Prince, 2004). For example, Ogunniyi et al. (2005) emphasised that, for older adults with dementia in Nigeria, support and care comes from the family, with limited public assistance.

With these contextual factors in mind, the social and economic implications of a rising AD prevalence are considerable. There are costs associated with medical care, social costs incurred by carers who are forced to stop work, and costs associated with informal care (Prince, 2004). Linked with these costs, and experienced in HICs and LAMICs, is the burden placed on the families and informal caregivers of patients with dementia; they are faced with overwhelming emotional and physical pressures (Clay, Roth, Wadley, & Haley, 2008; Gronning et al., 2013; Ogunniyi et al., 2005; Okoye & Asa, 2013; Richardson, Lee, Berg-Weger, & Grossberg, 2013).

Furthermore, older adults play an especially important role in South African society. In many cases, they help alleviate household financial strains by caring for (or even raising) grandchildren, caring for household members who are sick, disabled, or frail, and providing material and financial support for their offspring (Legido-Quigley, 2003). In particular, they care for family members affected by HIV/AIDS, and for the dependents of those family members (Ferreira, Keikelame, & Mosaval, 2001).

The valuable role that older adults play in South African society, therefore, highlights the importance of focusing on diseases that occur in this group. This study has contributed to awareness-creation around age-related cognitive impairment, and Alzheimer's disease, in South Africa. Creating awareness about these topics will be useful in assisting policymaking decisions in SA. AD research in South Africa (and in

LAMICs generally) has the potential for researchers and policy makers to work together to shape governmental policies for meeting the needs of its growing population of older adults. It is becoming increasingly obvious that a plan of action for AD in South Africa is urgently required. In the United States, a recent report (NIH Research Portfolio Online Reporting Tools, 2012) stated that in HICs, research funding from public sources for AD research is currently one-tenth of the funding for cancer research. It is likely that a similar, if not worse, trend is to be found in LAMICs such as South Africa. Raising awareness and thus promoting the profile of AD may boost funding for research into age-related neurodegenerative diseases of all kinds.

Creating awareness and enhanced understanding of AD is also important in dispelling the myths and superstitious beliefs that are commonly held about this disease, and therefore to reduce concealment of this disease as a result of these misconceptions (Kabir, Iliyasu, Abubakar, & Aliyu, 2004). Mental illness is still associated with significant stigma, and family members do not always encourage the pursuit of conventional treatment (Corrigan & Kleinlein, 2005). In Nigeria, it has been reported that in community-dwelling individuals, the preferred option in seeking treatment for mental illness is to visit spiritual and traditional healers, followed lastly by hospitals and Western medicine (Adewuya & Makanjuola, 2009).

In conversations with older adults, particularly those from rural and township areas, I was told that when older adults begin to behave oddly and become forgetful, they are sometimes cast out from the community, or they are hidden away by the family. These older adults are often considered to be bewitched or possessed. Studies have demonstrated that symptoms of mental illness are considered by members of the public and by traditional healers to be caused by supernatural factors (Adelekan, Makanjuola, & Ndom, 2001; Makanjuola, Adelekan, & Morakinyo, 2000). Such attitudes towards mental illness create a barrier to seeking health care. Furthermore, negative attitudes towards individuals with mental illness have been reported (Igbinomwanhia, James, & Omoaregba, 2013).The Alzheimer's Disease International World Alzheimer Report 2012 (Batsch & Mittelman, 2012) focused specifically on overcoming the stigma of dementia. Reducing the stigma associated with dementia is more likely to be achieved with well-developed and implemented political and public campaigns to encourage a society-level shift towards acceptance, inclusion, and proper treatment for people with dementia.

Methodological Limitations, Reflections, and Future Recommendations

No research study is without its difficulties and void of limitations; this one was no exception. Finding appropriate individuals to participate was not easy, particularly in the case of the AD patients. There were several reasons for this. First, I sought AD patients who were in the mild to moderate stages of the disease. This specificity was problematic because, in general, patients who present at the local memory and geriatric outpatient clinics are often already in the moderate-to-late stages of the disease. The reason for this relatively late presentation is that the early cognitive symptoms of AD are often regarded by individuals and their relatives as part of normal ageing. Only when there are challenging behavioural and difficult personality changes do patients (or, more often, their family members) seek medical attention. In some cases, even if the patient was willing to participate in this study, the family members were not keen for their relative to enroll in the study. This was sometimes due to the fact that there were logistic difficulties related to relatives or caregivers working full-time, with no-one available to accompany the individual to the study assessment (recall that a reliable informant was an inclusion criterion of the study). Sometimes, there were transport problems (e.g., a lack of access to personal transport). In such cases, where possible, we the research team, did our best to accommodate such individuals by arranging a personal driver to collect and return participants and their informants from their homes, and for a member of the research team to escort them between the hospital entrance and the clinic room.

In an attempt to overcome, or at least minimise, the difficulty I experienced in finding appropriate cases of patients with mild to moderate AD, I contacted GPs and asked if they were willing to assist by (a) allowing the research team to place approved advertisements in their practice rooms, and (b) referring potential early AD patients, with prior consent from the patient and his or her relative(s). Although GPs did not refer large numbers of AD patients, they were still a worthwhile recruitment source.

Another methodological limitation relates to psychosocial stress. This is, to some degree, an abstract concept; the experience of stress is entirely subjective, and there is great inter- and intra-individual variation in its experience. Although the stress measures I used in this study assessed a combination of lifetime and recent stress, as well as measuring the self-perceived impact of that stress, it is not certain that these measures captured the entirety of the participants' experiences of life stress. However,

the PSS and LTE-Q measures that I used have good psychometric properties, and the PSS, specifically, is the most widely used instrument for the appraisal of self-perceived current stress.

Even though stress itself is an abstract concept, the effects of stress can be measured physiologically. I used the collection of morning salivary cortisol to provide a general indicator of physiological stress. However, I encountered some difficulty in relation to the collection of the saliva samples using the salivette devices. Even though we provided participants with clear and simple instructions about how to collect their saliva samples using the salivettes, there were still errors. One such error included not chewing on the sponge long enough for it to absorb enough saliva. The saliva sample collection procedure was particularly problematic with AD patients who did not always have someone available to assist with collection of their samples. In addition, resource and financial constraints permitted the collection of only two salivary cortisol measurements per person for each visit. Future research may benefit from the collection of several measurements across the day. Lastly, due to a laboratory error, one batch of saliva samples was spoiled; thus accounting for the reduced number of cortisol samples at Time 1 and Time 2 in addition to the participant attrition.

The generalizability of the findings from this study to the South African population as a whole may be limited because the participants in this sample all resided in the Western Cape province of the country. As mentioned previously, the Western Cape is a heterogeneous population; population groups in the other provinces of the country may vary due to different lineages and migration patterns (Statistics South Africa, 2013). Furthermore, the Western Cape has been shown to have the highest prevalence of mental disorders, with anxiety disorders being the most common disorder, compared with the other provinces of South Africa (Herman et al., 2009). The findings from my study should, therefore, be interpreted with caution when attempting to generalize about cognitive ageing in South Africa, let alone all of Africa.

Although these methodological obstacles were challenging at the time, they provided opportunities to learn and encouraged creative thinking about how to adapt to these situations. One of the benefits of this study was that it contributed to raising awareness about AD in the local community. Many of the participants heard about the study by word of mouth: Friends or relatives were participating and, upon hearing about their participation, they too wanted to become involved. Most of the participants and informants involved in this study did not have much prior knowledge about AD; they

gained much through their involvement in the study. They understood better what the warning signs of AD are, what symptoms could be expected with disease progression, and whom they should consult with. Caregivers received advice about caring for patients with AD, and referrals to local support groups. Another positive point resulting from participation in the study was that some of the participants and/or their relatives felt that they had a voice in the context of a disease that was largely ignored in the South African public health sector. They appreciated that AD and its symptoms were not a normal part of ageing, that several symptoms were likely to occur, and that these symptoms were part of the disease and were not due to the patient being purposefully difficult. The latter enabled relatives and caregivers to be more tolerant and understanding towards the behaviours exhibited by the patient. So on an individual level, benefit from participation in this study appears to have been achieved.

Obviously, there should be further research in the area of age-related cognitive functioning and AD in South Africa, especially in light of increasing longevity. The general recommendation for future research would be to increase the Baseline sample size and increase the time of follow-up. In the case of a neurodegenerative disease such as AD, a longitudinal study design is likely to elicit the most useful and applicable findings. Ideally, this design should include a large number of older adults who are cognitively healthy at Baseline. Such a design element would allow for the determination of risk factors for cognitive impairment and AD by monitoring factors associated with conversion to AD.

Recommendations for future research also include tracking structural brain changes over time, with repeated MRI scans and measurement of hippocampal volumes. Had resources allowed, I should have liked to incorporate this design element into my study as it would have been useful to examine factors associated with hippocampal atrophy over time, instead of just at one cross-sectional measurement.

Due to financial constraints, I was only able to investigate plasma Aβ in a small sample of participants. The initial results from this investigation suggest that this is an area worth further exploration, particularly because obtaining blood samples for the determination of plasma Aβ concentrations is easier and less invasive than obtaining CSF. Specifically, it would be interesting to examine longitudinally whether an interaction between lower Aβ1-42/Aβ1-40 ratios and higher cortisol levels increases the risk for developing cognitive impairment and AD.

The stress-related findings in my study did not confirm *a priori* predictions. South Africa has high levels of crime and violence, and levels of psychosocial stress are high. Within this population, it might be useful to assess levels of psychosocial stress across several time points, to monitor changes in stress levels over time. A study that employs multiple measurements of cognition, and of physiological and psychological stress, over several years may detect relationships that the current analyses did not.

Summary and Conclusions

To my knowledge, this is the first African study to investigate psychosocial stress, cortisol, APOE-ϵ4, beta-amyloid, and hippocampal volume in a sample of older adults with and without cognitive impairment. It replicated established methods used in research studies emerging from high-income countries. The findings suggest that the Alzheimer's disease profile found in this sample of older adults from the Western Cape in South Africa is similar to that found in previously published studies, most of which have emerged from high-income countries in Europe and North America.

The conceptual framework upon which this study was based related to the multi-factorial profile of age-related cognitive impairment in older adults. The findings support the concept that several factors, to varying degrees, contribute to cognitive impairment and change in cognition over time. Increasing age and fewer years of education played the most prominent role in this regard. In the cross-sectional study, increasing age, fewer years of education, and presence of APOE-ϵ4 were significant predictors of cognitive functioning. However, when these factors were examined in the longitudinal study, they were not found to play a significant role in cognitive decline over a period of 3 years, although they contributed to cognitive change over that time period. This set of findings suggests that increasing age, lower education, and presence of APOE-ϵ4 may contribute to the development of the disease, but that once the disease process has begun, their role in predicting cognitive decline is less clear.

Stress, measured both subjectively (psychosocial) and objectively (physiological), was a focus of this research because it (a) has been shown to be associated with cognitive impairment and decline, and (b) was especially relevant to examine this factor in a LAMIC where the experience of psychosocial stress is known to be high. In the current sample, however, stress was not a significant predictor of Baseline cognitive functioning or subsequent cognitive change/decline. Although AD

patients did report higher levels of current psychosocial stress than controls, it remains an open question whether patients had higher levels of premorbid psychosocial stress, or whether they appraised their lives to be more stressful because they were experiencing the clinical symptoms of AD, such as memory loss and disorientation.

The beta-amyloid and hippocampal volume analyses, although performed for small subsets of participants, showed associations with cognition, and with stress in the case of beta-amyloid. These findings suggest that future research in these areas in this population might be worthwhile.

In conclusion, this study has set the platform for further research to be undertaken in this field and in this geographic context. This study has also gone some way toward creating awareness about age-related cognitive impairment and Alzheimer's disease in the Western Cape province of South Africa. The profile of factors associated with cognitive functioning in this sample of older South African adults was similar to that found in studies from high-income countries. In this sample, however, neither psychosocial nor physiological stress was related to Baseline cognitive function or to subsequent cognitive decline. The discrepancy between the findings reported here and the previously published findings in this area of the literature may relate to between-study variance in (a) the stage of disease in the AD patient samples, or (b) the way in which cortisol was measured (i.e., the time of day at which measurements were taken, or differences in the number of measurements taken).

This study provides novel information about South African older adults, and contributes more generally to knowledge about cognitive ageing and AD in low- and middle-income countries. Perhaps most importantly, the study highlights the importance for public health of understanding, treating, and (as far as possible) preventing age-associated cognitive disorders, particularly on a continent where they have largely been ignored.

References

Abercrombie, H. C., Kalin, N. H., Thurow, M. E., Rosenkranz, M. A., & Davidson, R. J. (2003). Cortisol variation in humans affects memory for emotionally laden and neutral information. *Behavioral Neuroscience*, *117*(3), 505-516.

Adelekan, M. L., Makanjuola, A. B., & Ndom, R. J. (2001). Traditional mental health practitioners in Kwara State, Nigeria. *East African Medical Journal*, *78*(4), 190-196.

Adewuya, A. & Makanjuola, R. (2009). Preferred treatment for mental illness among Southwestern Nigerians. *Psychiatric Services*, *60*(1), 121-124. doi:10.1176/appi.ps.60.1.121

Adhikari M. (2005). *Not white enough, not black enough: racial identity in the South African Coloured community.* Ohio: University Press.

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

Aguilera, G. (2011). HPA axis responsiveness to stress: implications for healthy aging. *Experimental Gerontology*, *46*(2-3), 90-95. doi:10.1016/j.exger.2010.08.023

Airaksinen, E., Larsson, M., Lundberg, I., & Forsell, Y. (2004). Cognitive functions in depressive disorders: evidence from a population-based study. *Psychological Medicine*, *34*(1), 83-91.

Albert, M. S., DeKosky, S. T., Dickson, D., Dubois, B., Feldman, H. H., Fox, N. C. et al. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers & Dementia*, *7*(3), 270-279. doi:10.1016/j.jalz.2011.03.008

Aldwin, C. M., Sutton, K. J., & Lachman, M. (1996). The development of coping resources in adulthood. *Journal of Personality*, *64*(4), 837-871.

Alkadhi, K. A. (2012). Chronic psychosocial stress exposes Alzheimer's disease phenotype in a novel at-risk model. *Frontiers in Bioscience (Elite edition)*, (*4)* 214-229.

Alkadhi, K. A., Alzoubi, K. H., Srivareerat, M., & Tran, T. T. (2012). Elevation of BACE in an Abeta rat model of Alzheimer's disease: exacerbation by chronic stress and prevention by nicotine. *International Journal of Neuropsychopharmacology*, *15*(2), 223-233. doi:10.1017/S1461145711000162

Alley, D., Suthers, K., & Crimmins, E. (2007). Education and Cognitive Decline in Older Americans: Results From the AHEAD Sample. *Research on Aging*, *29*(1), 73-94. doi:10.1177/0164027506294245

Almeida, D. M., Neupert, S. D., Banks, S. R., & Serido, J. (2005). Do daily stress processes account for socioeconomic health disparities? *Journals of Gerontology: Series B Psychological Sciences & Social Sciences, (2), 34-39.*

Alom, J., Llinares, I., & Fajardo, S. (2012). Clinical Approach to Diagnosis of Pre-Dementia Alzheimer's Disease (CAD-PAD). *Dementia and Geriatric Cognitive Disorders Extra, 2*(1), 332-342. doi:000341776

Alzheimer's Association. (2013). 2012 Alzheimer's Disease Facts and Figures. *Alzheimer's & Dementia, 8*(2), 1-72.

Alzheimer, A., Stelzmann, R. A., Schnitzlein, H. N., & Murtagh, F. R. (1995). An English translation of Alzheimer's 1907 paper, "Uber eine eigenartige Erkankung der Hirnrinde". *Clinical Anatomy, 8*(6), 429-431. doi:10.1002/ca.980080612

American Psychiatric Association. (2003). *Diagnostic and statistical manual of mental disorders.* (4th ed). Washington, DC: Author.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders*. (5th ed). Washington, DC: Author.

Andersen, K., Launer, L. J., Dewey, M. E., Letenneur, L., Ott, A., Copeland, J R., et al. (1999). Gender differences in the incidence of AD and vascular dementia: The EURODEM studies. EURODEM Incidence Research Group. *Neurology, 53*(9), 1992-1997.

Anderson, E. J., de Jager, C. A., & Iversen, S. D. (2006). The Placing Test: preliminary investigations of a quick and simple memory test designed to be sensitive to pre-dementia Alzheimer's disease but not to normal ageing. *Journal of Clinical and Experimental Neuropsychology, 28*(6), 843-858. doi:10.1080/13803390591001016

Apostolova, L. G., Green, A. E., Babakchanian, S., Hwang, K. S., Chou, Y. Y., Toga, A. W. et al. (2012). Hippocampal atrophy and ventricular enlargement in normal aging, mild cognitive impairment (MCI), and Alzheimer Disease. *Alzheimer Disease and Associated Disorders, 26*(1), 17-27. doi:10.1097/WAD.0b013e3182163b62

Ardila, A. (1995). Directions of research in cross-cultural neuropsychology. *Journal of Clinical and Experimental Neuropsychology, 17*(1), 143-150. doi:10.1080/13803399508406589

Arnsten, A. F. (2009). Stress signalling pathways that impair prefrontal cortex structure and function. *Nature Reviews Neuroscience, 10*(6), 410-422. doi:10.1038/nrn2648

Aston-Jones, G., Gonzalez, M., & Doran, S. (2007). Role of the locus coeruleus-norepinephrine system in arousal and circadian regulation of the sleep-wake cycle. In G. A. Ordway, M. A. Schwartz, & A. Frazer, (Eds.), *Brain norepinephrine: Neurobiology and therapeutics* (pp. 157-195). Cambridge University Press.

Austin, M. P., Mitchell, P., & Goodwin, G. M. (2001). Cognitive deficits in depression: possible implications for functional neuropathology. *British Journal of Psychiatry, 178,* 200-206.

Backman, L., Jones, S., Berger, A. K., Laukka, E. J., & Small, B. J. (2005). Cognitive impairment in preclinical Alzheimer's disease: a meta-analysis. *Neuropsychology, 19*(4), 520-531. doi:10.1037/0894-4105.19.4.520

Backman, L. & Small, B. J. (2007). Cognitive deficits in preclinical Alzheimer's disease and vascular dementia: patterns of findings from the Kungsholmen Project. *Physiology & Behaviour, 92*(1-2), 80-86. doi:10.1016/j.physbeh.2007.05.014

Baddeley, J. L. & Gros, D. F. (2013). Cognitive behavioral therapy for insomnia as a preparatory treatment for exposure therapy for posttraumatic stress disorder. *American Journal of Psychotherapy*, *67*(2), 203-214.

Baiyewu, O. & Potocnik, F. (2005). *Psychogeriatric services: current trends in Nigeria and South Africa.* New York: Oxford University Press.

Bajaj, J. S., Riggio, O., Allampati, S., Prakash, R., Gioia, S., Onori, E. et al. (2013). Cognitive Dysfunction Is Associated With Poor Socioeconomic Status in Patients With Cirrhosis: An International Multicenter Study. *Clinical Gastroenterology and Hepatology.* doi:10.1016/j.cgh.2013.05.010

Ballard, C., Gauthier, S., Corbett, A., Brayne, C., Aarsland, D., & Jones, E. (2011). Alzheimer's disease. *Lancet, 377*(9770), 1019-1031. doi:10.1016/S0140-6736(10)61349-9

Barber J. (1999). *South Africa in the twentieth century: A political history - in search of a nation state.* Wiley.

Barnes, D. E. & Yaffe, K. (2011). The projected effect of risk factor reduction on Alzheimer's disease prevalence. *Lancet Neurology, 10*(9), 819-828. doi:10.1016/S1474-4422(11)70072-2

Basso, M., Yang, J., Warren, L., MacAvoy, M. G., Varma, P., Bronen, R. A. et al. (2006). Volumetry of amygdala and hippocampus and memory performance in Alzheimer's disease. *Psychiatry Res*earch, *146*(3), 251-261.

Batsch, Y. & Mittelman, M. S. (2012). World Alzheimer Report 2012: Overcoming the stigma of dementia.

Batterham, P. J., Bunce, D., Cherbuin, N., & Christensen, H. (2013). Apolipoprotein E epsilon4 and Later-Life Decline in Cognitive Function and Grip Strength. *The American Journal of Geriatric Psychiatry,* doi:10.1016/j.jagp.2013.01.035

Baum, A., Cohen, L., & Hall, M. (1993). Control and intrusive memories as possible determinants of chronic stress. *Psychosomatic Medicine, 55*(3), 274-286.

Baum, A., Garofalo, J. P., & Yali, A. M. (1999). Socioeconomic status and chronic stress. Does stress account for SES effects on health? *Annals of the New York Academy of Sciences, 896,* 131-144.

Beard, C. M., Kokmen, E., Sigler, C., Smith, G. E., Petterson, T., & O'Brien, P. C. (1996). Cause of death in Alzheimer's disease. *Annals of Epidemiology*, *6*(3), 195-200. doi:1047279795000682

Bekaert, S., De, M. T., Rietzschel, E. R., De Buyzere, M. L., De, B. D., Langlois, M. et al. (2007). Telomere length and cardiovascular risk factors in a middle-aged population free of overt cardiovascular disease. *Aging Cell*, *6*(5), 639-647. doi:10.1111/j.1474-9726.2007.00321.x

Bemelmans, K. J., Noort, A., Rijk, R. D., Middelkoop, H. A. M., Kempen, G. M. J. V., & Goekoop, J. G. (2007). Plasma cortisol and norepinephrine in Alzheimer's disease: opposite relations with recall performance and stage of progression. *Acta Neuropsychiatrica*, *19*(4), 231-237. doi:10.1111/j.1601-5215.2006.00172.x.

Bennett, D. A., Wilson, R. S., Schneider, J. A., Evans, D. A., Aggarwal, N. T., Arnold, S. E. et al. (2003). Apolipoprotein E epsilon4 allele, AD pathology, and the clinical expression of Alzheimer's disease. *Neurology*, *60*(2), 246-252.

Berlau, D. J., Corrada, M. M., Head, E., & Kawas, C. H. (2009). APOE epsilon2 is associated with intact cognition but increased Alzheimer pathology in the oldest old. *Neurology*, *72*(9), 829-834.

Berridge, C. W. & Waterhouse, B. D. (2003). The locus coeruleus-noradrenergic system: modulation of behavioral state and state-dependent cognitive processes. *Brain Research Reviews*, *42*(1), 33-84.

Birditt, K. S., Fingerman, K. L., & Almeida, D. M. (2005). Age differences in exposure and reactions to interpersonal tensions: a daily diary study. *Psychology and Aging*, *20*(2), 330-340. doi:10.1037/0882-7974.20.2.330

Birks, J. & Harvey, R. J. (2006). Donepezil for dementia due to Alzheimer's disease. *The Cochrane Database of Systematic Reviews*, (1), CD001190. doi:10.1002/14651858.CD001190.pub2

Blackburn, E. H. (2000). Telomere states and cell fates. *Nature*, *408*(6808), 53-56. doi:10.1038/35040500

Bodnoff, S. R., Humphreys, A. G., Lehman, J. C., Diamond, D. M., Rose, G. M., & Meaney, M. J. (1995). Enduring effects of chronic corticosterone treatment on spatial learning, synaptic plasticity, and hippocampal neuropathology in young and mid-aged rats. *The Journal of Neuroscience*, *15*(1 Pt 1), 61-69.

Boeninger, D. K., Shiraishi, R. W., Aldwin, C. M., & Spiro, A. I. (2009). Why do older men report low stress ratings? Findings from the Veterans Affairs Normative Aging Study. *International Journal of Aging & Human Development*, *68*(2), 149-170.

Boone, K. B., Victor, T. L., Wen, J., Razani, J., & Ponton, M. (2007). The association between neuropsychological scores and ethnicity, language, and acculturation variables in a large patient population. *Archives of Clinical Neuropsychology*, *22*(3), 355-365. doi:10.1016/j.acn.2007.01.010

Braak, H. & Braak, E. (1991). Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathologica*, *82*(4), 239-259.

Braak, H. & Braak, E. (1995). Staging of Alzheimer's disease-related neurofibrillary changes. *Neurobiology of Aging*, *16*(3), 271-278.

Braaten, A. J., Parsons, T. D., McCue, R., Sellers, A., & Burns, W. J. (2006). Neurocognitive differential diagnosis of dementing diseases: Alzheimer's Dementia, Vascular Dementia, Frontotemporal Dementia, and Major Depressive Disorder. *International Journal of Neuroscience*, *116*(11), 1271-1293. doi:10.1080/00207450600920928

Brayne, C., Gill, C., Paykel, E. S., Huppert, F., & O'Connor, D. W. (1995). Cognitive decline in an elderly population--a two wave study of change. *Psychological Medicine*, *25*(4), 673-683.

Bremner, J. D. (2005). Effects of traumatic stress on brain structure and function: Relevance to early responses to trauma. *Journal of Trauma Dissociation*, *6*(2), 51-68.

Bremner, J. D. (2006). Stress and brain atrophy. *CNS & Neurological Disordisorders - Drug Targets*, *5*(5), 503-512.

Britt, W. G. I., Hansen, A. M., Bhaskerrao, S., Larsen, J. P., Petersen, F., Dickson, A. et al. (2011). Mild cognitive impairment: prodromal Alzheimer's disease or something else? *Journal of Alzheimer's Disease*, *27*(3), 543-551. doi:10.3233/JAD-2011-110740

Brooker, D. (2003). What is person-centred care in dementia? *Reviews in Clinical Gerontology*, *13*, 215-222. doi:10.1017/S095925980400108X

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

Brooks-Gunn, J. & Duncan, G. J. (1997). The effects of poverty on children. *The Future of Children*, *7*(2), 55-71.

Brugha, T. S. & Cragg, D. (1990). The List of Threatening Experiences: the reliability and validity of a brief life events questionnaire. *Acta Psychiatrica Scandinavica*, *82*(1), 77-81.

Bruwer, B., Emsley, R., Kidd, M., Lochner, C., & Seedat, S. (2008). Psychometric properties of the Multidimensional Scale of Perceived Social Support in youth. *Comprehensive Psychiatry*, *49*(2), 195-201.

Bu, G. (2009). Apolipoprotein E and its receptors in Alzheimer's disease: pathways, pathogenesis and therapy. *Nature Reviews Neuroscience*, *10*(5), 333-344. doi:10.1038/nrn2620

Buckner, R. L., Head, D., Parker, J., Fotenos, A. F., Marcus, D., Morris, J. C. et al. (2004). A unified approach for morphometric and functional data analysis in

young, old, and demented adults using automated atlas-based head size normalization: reliability and validation against manual measurement of total intracranial volume. *Neuroimage*, *23*(2), 724-738. doi:10.1016/j.neuroimage.2004.06.018

Bucks, R. S., Ashworth, D. L., Wilcock, G. K., & Siegfried, K. (1996). Assessment of activities of daily living in dementia: development of the Bristol Activities of Daily Living Scale. *Age and Ageing*, *25*(2), 113-120.

Bunce, D., Bielak, A. A., Anstey, K. J., Cherbuin, N., Batterham, P. J., & Easteal, S. (2013). APOE genotype and cognitive change in young, middle-aged, and older adults living in the community. *The Journals of Gerontology: Series A, Biological Sciences and Medical Sciences*, doi:10.1093/gerona/glt103

Bunce, D., Fratiglioni, L., Small, B. J., Winblad, B., & Backman, L. (2004). APOE and cognitive decline in preclinical Alzheimer disease and non-demented aging. *Neurology*, *63*(5), 816-821.

Butler, S. M., Ashford, J. W., & Snowdon, D. A. (1996). Age, education, and changes in the Mini-Mental State Exam scores of older women: findings from the Nun Study. *Journal of the American Geriatrics Society*, *44*(6), 675-681.

Butler, S. M. & Snowdon, D. A. (1996). Trends in mortality in older women: findings from the Nun Study. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, *51*(4), S201-S208.

Callahan, C. M., Hall, K. S., Hui, S. L., Musick, B. S., Unverzagt, F. W., & Hendrie, H. C. (1996). Relationship of age, education, and occupation with dementia among a community-based sample of African Americans. *Archives of Neurology*, *53*(2), 134-140.

Cannon W. B. (1932). *The wisdom of the body.* New York: Norton & Company Inc.

Capper, R., Britt-Compton, B., Tankimanova, M., Rowson, J., Letsolo, B., Man, S. et al. (2007). The nature of telomere fusion and a definition of the critical telomere length in human cells. *Genes & Development*, *21*(19), 2495-2508. doi:21/19/2495

Carroll, J. C., Iba, M., Bangasser, D. A., Valentino, R. J., James, M. J., Brunden, K. R. et al. (2011). Chronic stress exacerbates tau pathology, neurodegeneration, and cognitive performance through a corticotropin-releasing factor receptor-dependent mechanism in a transgenic mouse model of tauopathy. *Journal of Neuroscience*, *31*(40), 14436-14449. doi:10.1523/JNEUROSCI.3836-11.2011

Carvalho-Wells, A. L., Jackson, K. G., Lockyer, S., Lovegrove, J. A., & Minihane, A. M. (2012). APOE genotype influences triglyceride and C-reactive protein responses to altered dietary fat intake in UK adults. *American Journal of Clinical Nutrition*, *96*(6), 1447-1453. doi:10.3945/ajcn.112.043240

Caswell, L. W., Vitaliano, P. P., Croyle, K. L., Scanlan, J. M., Zhang, J., & Daruwala, A. (2003). Negative associations of chronic stress and cognitive performance in

older adult spouse caregivers. *Experimental Aging Research*, *29*(3), 303-318. doi:10.1080/03610730303721

Catania, C., Sotiropoulos, I., Silva, R., Onofri, C., Breen, K. C., Sousa, N. et al. (2009). The amyloidogenic potential and behavioral correlates of stress. *Molecular Psychiatry*, *14*(1), 95-105. doi:10.1038/sj.mp.4002101

Caughey, B. & Lansbury, P. T. (2003). Protofibrils, pores, fibrils, and neurodegeneration: separating the responsible protein aggregates from the innocent bystanders. *Molecular Psychiatry*, *26*, 267-298. doi:10.1146/annurev.neuro.26.010302.081142

Chandra, V., Ganguli, M., Pandav, R., Johnston, J., Belle, S., & DeKosky, S. T. (1998). Prevalence of Alzheimer's disease and other dementias in rural India: the Indo-US study. *Neurology*, *51*(4), 1000-1008.

Chaplin, T. M., Hong, K., Bergquist, K., & Sinha, R. (2008). Gender differences in response to emotional stress: an assessment across subjective, behavioral, and physiological domains and relations to alcohol craving. *Alcoholism, Clinical and Experimental Research*, *32*(7), 1242-1250. doi:10.1111/j.1530-0277.2008.00679.x

Chapman, R. M., Mapstone, M., Porsteinsson, A. P., Gardner, M. N., McCrary, J. W., Degrush, E. et al. (2010). Diagnosis of Alzheimer's disease using neuropsychological testing improved by multivariate analyses. *Journal of Clinical and Experimental Neuropsychology*, *32*(8), 793-808. doi:10.1080/13803390903540315

Charmandari, E., Tsigos, C., & Chrousos, G. (2005). Endocrinology of the stress response. *Annual Review of Physiology*, *67*259-284. doi:10.1146/annurev.physiol.67.040403.120816

Charney, D. S. (2004). Psychobiological mechanisms of resilience and vulnerability: implications for successful adaptation to extreme stress. *American Journal of Psychiatry*, *161*(2), 195-216.

Chavey, W. E. (2000). The importance of beta blockers in the treatment of heart failure. *American Family Physician*, *62*(11), 2453-2462.

Childress, J. E., McDowell, E. J., Dalai, V. V., Bogale, S. R., Ramamurthy, C., Jawaid, A. et al. (2013). Hippocampal volumes in patients with chronic combat-related posttraumatic stress disorder: a systematic review. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *25*(1), 12-25. doi:10.1176/appi.neuropsych.12010003

Chintamaneni, M. & Bhaskar, M. (2012). Biomarkers in Alzheimer's disease: a review. *ISRN Pharmacology*, *2012*, doi:10.5402/2012/984786

Chui, H. C., Zheng, L., Reed, B. R., Vinters, H. V., & Mack, W. J. (2012). Vascular risk factors and Alzheimer's disease: are these risk factors for plaques and tangles or for concomitant vascular pathology that increases the likelihood of

dementia? An evidence-based review. *Alzheimers Research & Therapy*, *4*(1), 1. doi:10.1186/alzrt98

Cipolotti, L., Shallice, T., Chan, D., Fox, N., Scahill, R., Harrison, G. et al. (2001). Long-term retrograde amnesia...the crucial role of the hippocampus. *Neuropsychologia*, *39*(2), 151-172.

Clay, O. J., Roth, D. L., Wadley, V. G., & Haley, W. E. (2008). Changes in social support and their impact on psychosocial outcome over a 5-year period for African American and White dementia caregivers. *International Journal of Geriatric Psychiatry*, *23*(8), 857-862. doi:10.1002/gps.1996

Cohen J. E. (1988). *Statistical Power Analysis for the Behavioral Sciences.* Hillsdale, NJ: Lawrence Erlbaum Associates.

Cohen, S. & Janicki-Deverts, D. (2012). Who's stressed? Distributions of psychological stress in the United States in probability samples from 1983, 2006 and 2009. *Journal of Applied Social Psychology*, *42*(6), 1320-1334.

Cohen, S., Kamarck, T., & Mermelstein, R. (1983). A global measure of perceived stress. *Journal of Health and Social Behavior*, *24*(4), 385-396.

Cohen, S., Kessler, R. C., & Gordon, L. G. (1995). Strategies for measuring stress in studies of psychiatric and physical disorders. In *Measuring Stress: A Guide for Health and Social Scientists* (pp. 3-28) New York: Oxford University Press.

Cohen, S. & Wills, T. A. (1985). Stress, social support, and the buffering hypothesis. *Psychological Bulletin*, *98*(2), 310-357.

Conde-Sala, J. L., Rene-Ramirez, R., Turro-Garriga, O., Gascon-Bayarri, J., Campdelacreu-Fumado, J., Juncadella-Puig, M. et al. (2013). Severity of Dementia, Anosognosia, and Depression in Relation to the Quality of Life of Patients With Alzheimer Disease: Discrepancies Between Patients and Caregivers. *The American Journal of Geriatric Psychiatry*, doi:10.1016/j.jagp.2012.07.001

Connor, K. M. & Davidson, J. R. (2003). Development of a new resilience scale: the Connor-Davidson Resilience Scale (CD-RISC). *Depression and Anxiety*, *18*(2), 76-82. doi:10.1002/da.10113

Corbett, E. L., Steketee, R. W., ter Kuile, F. O., Latif, A. S., Kamali, A., & Hayes, R. J. (2002). HIV-1/AIDS and the control of other infectious diseases in Africa. *Lancet*, *359*(9324), 2177-2187. doi:10.1016/S0140-6736(02)09095-5

Corbo, R. M. & Scacchi, R. (1999). Apolipoprotein E (APOE) allele distribution in the world. Is APOE*4 a 'thrifty' allele? *Annals of Human Genetics*, *63*(Pt 4), 301-310.

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

Corrada, M. M., Brookmeyer, R., Paganini-Hill, A., Berlau, D., & Kawas, C. H. (2010). Dementia incidence continues to increase with age in the oldest old: the 90+ study. *Annals of Neurology, 67*(1), 114-121. doi:10.1002/ana.21915

Corrigan, P. W. & Kleinlein, P. (2005). The impact of mental illness stigma. In *On the stigma of mental illness: practical strategies for research and social change* (11-44) Washington, DC: American Psychological Association.

Cosentino, S., Scarmeas, N., Helzner, E., Glymour, M. M., Brandt, J., Albert, M. et al. (2008). APOE epsilon 4 allele predicts faster cognitive decline in mild Alzheimer disease. *Neurology, 70*(19 Pt 2), 1842-1849. doi:10.1212/01.wnl.0000304038.37421.cc

Cottraux, J. (2002). Nonpharmacological treatments for anxiety disorders. *Dialogues in Clinical Neuroscience, 4*(3), 305-319.

Crews, L. & Masliah, E. (2010). Molecular mechanisms of neurodegeneration in Alzheimer's disease. *Human Molecular Genetics, 19*(1), 12-20. doi:10.1093/hmg/ddq160

Csernansky, J. G., Dong, H., Fagan, A. M., Wang, L., Xiong, C., Holtzman, D. M. et al. (2006). Plasma cortisol and progression of dementia in subjects with Alzheimer-type dementia. *American Journal of Psychiatry, 163*(12), 2164-2169. doi:10.1176/appi.ajp.163.12.2164

Cullum, S., Huppert, F. A., McGee, M., Dening, T., Ahmed, A., Paykel, E. S. et al. (2000). Decline across different domains of cognitive function in normal ageing: results of a longitudinal population-based study using CAMCOG. *International Journal of Geriatric Psychiatry, 15*(9), 853-862. doi:10.1002/1099-1166(200009)15:9

Currie, J. (2005). Health disparities and gaps in school readiness. *Future Child, 15*(1), 117-138.

Dale, A. M., Fischl, B., & Sereno, M. I. (1999). Cortical surface-based analysis. I. Segmentation and surface reconstruction. *NeuroImage., 9*(2), 179-194.

Damian, M., Hausner, L., Jekel, K., Richter, M., Froelich, L., Almkvist, O. et al. (2013). Single-Domain Amnestic Mild Cognitive Impairment Identified by Cluster Analysis Predicts Alzheimer's Disease in the European Prospective DESCRIPA Study. *Dementia and Geriatric Cognitive Disorders, 36*(1-2), 1-19. doi:10.1159/000348354

Daniel, M., Moore, D. S., Decker, S., Belton, L., DeVellis, B., Doolen, A. et al. (2006). Associations among education, cortisol rhythm, and BMI in blue-collar women. *Obesity (Silver Spring), 14*(2), 327-335. doi:14/2/327

Daviglus, M. L., Bell, C. C., Berrettini, W., Bowen, P. E., Connolly, E. S., Jr., Cox, N. J. et al. (2010). National Institutes of Health State-of-the-Science Conference statement: preventing alzheimer disease and cognitive decline. *Annals of Internal Medicine, 153*(3), 176-181. doi:10.1059/0003-4819-153-3-201008030-00260

de Craen, A. J., Heeren, T. J., & Gussekloo, J. (2003). Accuracy of the 15-item geriatric depression scale (GDS-15) in a community sample of the oldest old. *International Journal of Geriatric Psychiatry, 18*(1), 63-66. doi:10.1002/gps.773

de Jager, C. A., Hogervorst, E., Combrinck, M., & Budge, M. M. (2003). Sensitivity and specificity of neuropsychological tests for mild cognitive impairment, vascular cognitive impairment and Alzheimer's disease. *Psychological Medicine, 33*(6), 1039-105.

de Kloet, E. R., Datson, N. A., Revsin, Y., Champagne, D. L., & Oitzl, M. S. (2008). Brain corticosteroid receptor function in response to psychosocial stressors. In D. W. Pfaff, C. Kordon, P. Chanson, & Y. Christen, (Eds.), *Hormones and Social Behaviour* (131-150) Berlin: Springer.

de Kloet, E. R., Joels, M., & Holsboer, F. (2005). Stress and the brain: from adaptation to disease. *Nature Reviews Neuroscience, 6*(6), 463-475. doi:nrn1683

de Quervain, D. J., Aerni, A., Schelling, G., & Roozendaal, B. (2009). Glucocorticoids and the regulation of memory in health and disease. *Frontiers in Neuroendocrinoology, 30*(3), 358-370. doi:10.1016/j.yfrne.2009.03.002

de Quervain, D. J., Henke, K., Aerni, A., Coluccia, D., Wollmer, M. A., Hock, C. et al. (2003). A functional genetic variation of the 5-HT2a receptor affects human memory. *Nature Neuroscience, 6*(11), 1141-1142. doi:10.1038/nn1146

Deuschle, M., Gotthardt, U., Schweiger, U., Weber, B., Korner, A., Schmider, J. et al. (1997). With aging in humans the activity of the hypothalamus-pituitary-adrenal system increases and its diurnal amplitude flattens. *Life Sciences, 61*(22), 2239-2246.

de Wit, E., Delport, W., Rugamika, C. E., Meintjes, A., Moller, M., van Helden, P. D. et al. (2010). Genome-wide analysis of the structure of the South African Coloured Population in the Western Cape. *Human Genetics, 128*(2), 145-153. doi:10.1007/s00439-010-0836-1

Di, C. A., Baldereschi, M., Amaducci, L., Lepore, V., Bracco, L., Maggi, S. et al. (2002). Incidence of dementia, Alzheimer's disease, and vascular dementia in Italy. The ILSA Study. *Journal of the American Geriatrics Society, 50*(1), 41-48.

Diamond, D. M., Bennett, M. C., Fleshner, M., & Rose, G. M. (1992). Inverted-U relationship between the level of peripheral corticosterone and the magnitude of hippocampal primed burst potentiation. *Hippocampus, 2*(4), 421-430. doi:10.1002/hipo.450020409

Dickerson, S. S., Gruenewald, T. L., & Kemeny, M. E. (2004). When the social self is threatened: shame, physiology, and health. *Journal of Personality, 72*(6), 1191-1216. doi:10.1111/j.1467-6494.2004.00295

Dickerson, S. S. & Kemeny, M. E. (2004). Acute stressors and cortisol responses: a theoretical integration and synthesis of laboratory research. *Psychol.Bull.*, *130*(3), 355-391. doi:10.1037/0033-2909.130.3.355

Dik, M. G., Jonker, C., Bouter, L. M., Geerlings, M. I., van Kamp, G. J., & Deeg, D. J. (4-11-2000). APOE-epsilon4 is associated with memory decline in cognitively impaired elderly. *Neurology*, *54*(7), 1492-1497.

Dodt, C., Breckling, U., Derad, I., Fehm, H. L., & Born, J. (1997). Plasma epinephrine and norepinephrine concentrations of healthy humans associated with nighttime sleep and morning arousal. *Hypertension*, *30*(1 Pt 1), 71-76.

Dolan, D., Troncoso, J., Resnick, S. M., Crain, B. J., Zonderman, A. B., & O'Brien, R. J. (2010). Age, Alzheimer's disease and dementia in the Baltimore Longitudinal Study of Ageing. *Brain*, *133*(8), 2225-2231. doi:10.1093/brain/awq141

Dong, H. & Csernansky, J. G. (2009). Effects of stress and stress hormones on amyloid-beta protein and plaque deposition. *Journal of Alzheimer's disease*, *18*(2), 459-469. doi:10.3233/JAD-2009-1152

Dorn, L. D., Lucke, J. F., Loucks, T. L., & Berga, S. L. (2007). Salivary cortisol reflects serum cortisol: analysis of circadian profiles. *Annals of Clinical Biochemistry*, *44*(Pt 3), 281-284. doi:10.1258/000456307780480954

Dowse, R. & Ehlers, M. S. (2001). The evaluation of pharmaceutical pictograms in a low-literate South African population. *Patient Education and Counseling*, *45*(2), 87-99.

Drago, V., Babiloni, C., Bartres-Faz, D., Caroli, A., Bosch, B., Hensch, T. et al. (2011). Disease tracking markers for Alzheimer's disease at the prodromal (MCI) stage. *Journal of Alzheimer's Disease*, *26 Suppl 3*, 159-199. doi:10.3233/JAD-2011-0043

Dregan, A., Stewart, R., & Gulliford, M. C. (2013). Cardiovascular risk factors and cognitive decline in adults aged 50 and over: a population-based cohort study. *Age and Ageing*, *42*(3), 338-345. doi:10.1093/ageing/afs166

Dubois, B., Feldman, H. H., Jacova, C., DeKosky, S. T., Barberger-Gateau, P., Cummings, J. et al. (2007b). Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. *Lancet Neurology*, *6*(8), 734-746. doi:10.1016/S1474-4422(07)70178-3

Duman, R. S. (2005). Neurotrophic factors and regulation of mood: role of exercise, diet and metabolism. *Neurobiology of Aging*, *26 Suppl 1*, 88-93. doi:10.1016/j.neurobiolaging.2005.08.018

Eichenbaum, H. (2003). How does the hippocampus contribute to memory? *Trends in Cognitive Sciences*, *7*(10), 427-429.

Engel, G. L. (1977). The need for a new medical model: a challenge for biomedicine. *Science*, *196*(4286), 129-136.

Epel, E., Lapidus, R., McEwen, B., & Brownell, K. (2001). Stress may add bite to appetite in women: a laboratory study of stress-induced cortisol and eating behavior. *Psychoneuroendocrinology*, *26*(1), 37-49.

Epel, E. S., Blackburn, E. H., Lin, J., Dhabhar, F. S., Adler, N. E., Morrow, J. D. et al. (2004). Accelerated telomere shortening in response to life stress. *Proceedings of the National Academy of Sciences of the United States of America*, *101*(49), 17312-17315. doi:10.1073/pnas.0407162101

Evans, D. A., Bennett, D. A., Wilson, R. S., Bienias, J. L., Morris, M. C., Scherr, P. A. et al. (2003). Incidence of Alzheimer disease in a biracial urban community: relation to apolipoprotein E allele status. *Archives of Neurology*, *60*(2), 185-189.

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

Farrag, A., Farwiz, H. M., Khedr, E. H., Mahfouz, R. M., & Omran, S. M. (1998). Prevalence of Alzheimer's disease and other dementing disorders: Assiut-Upper Egypt study. *Dementia and Geriatric Cognitive Disorders*, *9*(6), 323-328.

Farrer, L. A., Cupples, L. A., Haines, J. L., Hyman, B., Kukull, W. A., Mayeux, R. et al. (1997). Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. T*he Journal of the American Medical Association*, *278*(16), 1349-1356.

Fast, N. J., Gruenfeld, D. H., Sivanathan, N., & Galinsky, A. D. (2009). Illusory control: a generative force behind power's far-reaching effects. *Psychological Science*, *20*(4), 502-508. doi:10.1111/j.1467-9280.2009.02311.x

Fernandez, M., Gobartt, A. L., & Balana, M. (2010). Behavioural symptoms in patients with Alzheimer's disease and their association with cognitive impairment. *BMC Neurology*, *10*(87). doi:10.1186/1471-2377-10-87

Ferrari, E., Arcaini, A., Gornati, R., Pelanconi, L., Cravello, L., Fioravanti, M. et al. (2000). Pineal and pituitary-adrenocortical function in physiological aging and in senile dementia. *Experimental Gerontology*, *35*(9-10), 1239-1250.

Ferreira M., Keikelame, M. J., & Mosaval, Y. (2001). *Older women as carers to children and grandchildren affected by AIDS: A study towards supporting the carers.* Cape Town: Institute of Ageing in Africa, Faculty of Health Science, University of Cape Town.

Ferretti, L., McCurry, S. M., Logsdon, R., Gibbons, L., & Teri, L. (2001). Anxiety and Alzheimer's disease. *Journal of Geriatric Psychiatry and Neurology*, *14*(1), 52-58.

Ferri, C. P., Prince, M., Brayne, C., Brodaty, H., Fratiglioni, L., Ganguli, M. et al. (2005). Global prevalence of dementia: a Delphi consensus study. *Lancet*, *366*(9503), 2112-2117. doi:10.1016/S0140-6736(05)67889-0

Ferstl, E. C. (2006). Text comprehension in middle aged adults: is there anything wrong? *Neuropsychology, Development, and Cognition: Section B, Aging, Neuropsychology and Cognition*, *13*(1), 62-85. doi:10.1080/13825580490904237

Figurski, M. J., Waligorska, T., Toledo, J., Vanderstichele, H., Korecka, M., Lee, V. M. et al. (2012). Improved protocol for measurement of plasma beta-amyloid in longitudinal evaluation of Alzheimer's Disease Neuroimaging Initiative study patients. *Alzheimers & Dementia*, *8*(4), 250-260. doi:10.1016/j.jalz.2012.01.001

Finchilescu, G. & Dawes, A. (1999). Adolescents' future ideologies through four decades of South African history. *Social Dynamics: A journal of African studies*, *25*(2), 98-118. doi:10.1080/02533959908458677

Fischl, B. (2012). FreeSurfer. *NeuroImage.*, *62*(2), 774-781.

Fischl, B. & Dale, A. M. (2000). Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proceedings of the National Academy of Sciences U.S.A*, *97*(20), 11050-11055. doi:10.1073/pnas.200033797

Fischl, B., Liu, A., & Dale, A. M. (2001). Automated manifold surgery: constructing geometrically accurate and topologically correct models of the human cerebral cortex. *IEEE Transactions on Medical Imaging*, *20*(1), 70-80. doi:10.1109/42.906426

Fischl, B., Salat, D. H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C. et al. (2002). Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron*, *33*(3), 341-355.

Fischl, B., Salat, D. H., van der Kouwe, A. J., Makris, N., Segonne, F., Quinn, B. T. et al. (2004a). Sequence-independent segmentation of magnetic resonance images. *Neuroimage (23)*, Supplement 1, 69-84.

Fischl, B., van der Kouwe, A., Destrieux, C., Halgren, E., Segonne, F., Salat, D. H. et al. (2004b). Automatically parcellating the human cerebral cortex. *Cerebral Cortex*, *14*(1), 11-22.

Florent-Bechard, S., Desbene, C., Garcia, P., Allouche, A., Youssef, I., Escanye, M. C. et al. (2009). The essential role of lipids in Alzheimer's disease. *Biochimie*, *91*(6), 804-809. doi:10.1016/j.biochi.2009.03.004

Foley, P. & Kirschbaum, C. (2010). Human hypothalamus-pituitary-adrenal axis responses to acute psychosocial stress in laboratory settings. *Neuroscience and Biobehavioral Reviews*, *35*(1), 91-96. doi:10.1016/j.neubiorev.2010.01.010

Fotenos, A. F., Snyder, A. Z., Girton, L. E., Morris, J. C., & Buckner, R. L. (2005). Normative estimates of cross-sectional and longitudinal brain volume decline in aging and AD. *Neurology*, *64*(6), 1032-1039. doi:10.1212/01.WNL.0000154530.72969.11

Frankenberg, E., Sikoki, B., Sumantri, C., & Thomas, D. (2013). Education, vulnerability, and resilience after a natural disaster. *Ecology and Society*, *18*(2), 16. doi:10.5751/ES-05377-180216

Frisoni, G. B., Fox, N. C., Jack, C. R., Jr., Scheltens, P., & Thompson, P. M. (2010). The clinical use of structural MRI in Alzheimer disease. *Nature Reviews Neurology*, *6*(2), 67-77. doi:10.1038/nrneurol.2009.215

Frisoni, G. B., Testa, C., Sabattoli, F., Beltramello, A., Soininen, H., & Laakso, M. P. (2005). Structural correlates of early and late onset Alzheimer's disease: voxel based morphometric study. *Journal of Neurology, Neurosurgery & Psychiatry*, *76*(1), 112-114. doi:10.1136/jnnp.2003.029876

Fritsch, T., Smyth, K. A., Debanne, S. M., Petot, G. J., & Friedland, R. P. (2005). Participation in novelty-seeking leisure activities and Alzheimer's disease. *Journal of Geriatric Psychiatry and Neurology*, *18*(3), 134-141. doi:18/3/134 [pii];10.1177/0891988705277537 [doi]

Galasko, D., Golde, T. E., & Scheltens, P. (2013). Progress in Alzheimer's disease research circa 2013: Is the glass half empty or half full? *Alzheimer's Research & Therapy*, *5*(3), 26. doi:10.1186/alzrt180

Gallardo, G., Schluter, O. M., & Sudhof, T. C. (2008). A molecular pathway of neurodegeneration linking alpha-synuclein to ApoE and Abeta peptides. *Nature Neuroscience*, *11*(3), 301-308. doi:10.1038/nn2058

Ganguli, M., Du, Y., Dodge, H. H., Ratcliff, G. G., & Chang, C. C. (2006). Depressive symptoms and cognitive decline in late life: a prospective epidemiologial study. *Archives of General Psychiatry*, *63*(2), 153-160.

Ganguli, M., Snitz, B. E., Lee, C. W., Vanderbilt, J., Saxton, J. A., & Chang, C. C. (2010). Age and education effects and norms on a cognitive test battery from a population-based cohort: the Monongahela-Youghiogheny Healthy Aging Team. *Aging & Mental Health*, *14*(1), 100-107. doi:10.1080/13607860903071014

Gao, S., Hendrie, H. C., Hall, K. S., & Hui, S. (1998). The relationships between age, sex, and the incidence of dementia and Alzheimer disease: a meta-analysis. *Archives of General Psychiatry*, *55*(9), 809-815.

Gatz, M., Reynolds, C. A., Fratiglioni, L., Johansson, B., Mortimer, J. A., Berg, S. et al. (2006). Role of genes and environments for explaining Alzheimer disease. *Archives of General Psychiatry*, *63*(2), 168-174. doi:10.1001/archpsyc.63.2.168

Gatz, M., Svedberg, P., Pedersen, N. L., Mortimer, J. A., Berg, S., & Johansson, B. (2001). Education and the risk of Alzheimer's disease: findings from the study of dementia in Swedish twins. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, *56*(5), 292-300.

Gauthier, S., Cummings, J., Ballard, C., Brodaty, H., Grossberg, G., Robert, P. et al. (2010). Management of behavioral problems in Alzheimer's disease.

International Psychogeriatrics, *22*(3), 346-372. doi:10.1017/S1041610209991505

Geda, Y. E., Knopman, D. S., Mrazek, D. A., Jicha, G. A., Smith, G. E., Negash, S. et al. (2006). Depression, apolipoprotein E genotype, and the incidence of mild cognitive impairment: a prospective cohort study. *Archives of Neurology*, *63*(3), 435-440. doi:10.1001/archneur.63.3.435

George-Carey, R., Adeloye, D., Chan, K. Y., Paul, A., Kolcic, I., Campbell, H. et al. (2012). An estimate of the prevalence of dementia in Africa: A systematic analysis. *Journal of Global Health*, *2*(2), 20401. doi:10.7189/jogh.02.020401

Geroldi, C., Pihlajamaki, M., Laakso, M. P., DeCarli, C., Beltramello, A., Bianchetti, A. et al. (1999). APOE-epsilon4 is associated with less frontal and more medial temporal lobe atrophy in AD. *Neurology*, *53*(8), 1825-1832.

Gerritsen, L., Comijs, H. C., Deeg, D. J., Penninx, B. W., & Geerlings, M. I. (2011). Salivary cortisol, APOE-epsilon4 allele and cognitive decline in a prospective study of older persons. *Neurobiology of Aging*, *32*(9), 1615-1625. doi:10.1016/j.neurobiolaging.2009.09.007

Gilbertson, M. W., Shenton, M. E., Ciszewski, A., Kasai, K., Lasko, N. B., Orr, S. P. et al. (2002). Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. *Nature Neuroscience*, *5*(11), 1242-1247. doi:10.1038/nn958

Gilman, S. E., Trinh, N. H., Smoller, J. W., Fava, M., Murphy, J. M., & Breslau, J. (2013). Psychosocial stressors and the prognosis of major depression: a test of Axis IV. *Psychological Medicine, 43*(2), 303-316. doi:S0033291712001080

Giubilei, F., Patacchioli, F. R., Antonini, G., Sepe, M. M., Tisei, P., Bastianello, S. et al. (2001). Altered circadian cortisol secretion in Alzheimer's disease: clinical and neuroradiological aspects. *Journal of Neuroscience Research*, *66*(2), 262-265. doi:10.1002/jnr.1219

Gold, C. A. & Budson, A. E. (2008). Memory loss in Alzheimer's disease: implications for development of therapeutics. *Expert Review of Neurotherapeutics*, *8*(12), 1879-1891. doi:10.1586/14737175.8.12.1879

Goldman, N., Glei, D. A., Seplaki, C., Liu, I. W., & Weinstein, M. (2005). Perceived stress and physiological dysregulation in older adults. *Stress*, *8*(2), 95-105. doi:10.1080/10253890500141905

Gomar, J. J., Bobes-Bascaran, M. T., Conejero-Goldberg, C., Davies, P., & Goldberg, T. E. (2011). Utility of combinations of biomarkers, cognitive markers, and risk factors to predict conversion from mild cognitive impairment to Alzheimer disease in patients in the Alzheimer's disease neuroimaging initiative. *Archives of General Psychiatry*, *68*(9), 961-969. doi:10.1001/archgenpsychiatry.2011.96

Gooding, P. A., Hurst, A., Johnson, J., & Tarrier, N. (2012). Psychological resilience in young and older adults. *International Journal Geriatric Psychiatry*, *27*(3), 262-270. doi:10.1002/gps.2712

Gouin, J. P., Hantsoo, L., & Kiecolt-Glaser, J. K. (2008). Immune dysregulation and chronic stress among older adults: a review. *Neuroimmunomodulation*, *15*(4-6), 251-259. doi:10.1159/000156468

Graff-Radford, N. R., Crook, J. E., Lucas, J., Boeve, B. F., Knopman, D. S., Ivnik, R. J. et al. (2007). Association of low plasma Abeta42/Abeta40 ratios with increased imminent risk for mild cognitive impairment and Alzheimer disease. *Archives of Neurology*, *64*(3), 354-362. doi:10.1001/archneur.64.3.354

Granath, J., Ingvarsson, S., von, T. U., & Lundberg, U. (2006). Stress management: a randomized study of cognitive behavioural therapy and yoga. *Cognitive Behaviour Therapy*, *35*(1), 3-10. doi:10.1080/16506070500401292

Green, K. N., Billings, L. M., Roozendaal, B., McGaugh, J. L., & LaFerla, F. M. (2006). Glucocorticoids increase amyloid-beta and tau pathology in a mouse model of Alzheimer's disease. *The Journal of Neuroscience*, *26*(35), 9047-9056. doi:10.1523/JNEUROSCI.2797-06.2006

Green, R. C., Cupples, L. A., Go, R., Benke, K. S., Edeki, T., Griffith, P. A. et al. (2002). Risk of dementia among white and African American relatives of patients with Alzheimer disease. *Journal of the American Medical Association*, *287*(3), 329-336.

Greenwood, P. M. (2000). The frontal aging hypothesis evaluated. *Journal of the International Neuropsychological Society*, *6*(6), 705-726.

Greiner, P. A., Snowdon, D. A., & Greiner, L. H. (1996). The relationship of self-rated function and self-rated health to concurrent functional ability, functional decline, and mortality: findings from the Nun Study. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, *51*(5), S234-S241.

Gronning, H., Kristiansen, S., Dyre, D., Rahmani, A., Gyllenborg, J., & Hogh, P. (2013). Caregiver burden and psychosocial services in patients with early and late onset Alzheimer's disease. *Danish Medical Journal*, *60*(7), A4649.

Grzywacz, J. G., Almeida, D. M., Neupert, S. D., & Ettner, S. L. (2004). Socioeconomic status and health: a micro-level analysis of exposure and vulnerability to daily stressors. *Journal of Health and Social Behavior*, *45*(1), 1-16.

Guerchet, M., Houinato, D., Paraiso, M. N., von, A. N., Nubukpo, P., Otto, M. et al. (2009). Cognitive impairment and dementia in elderly people living in rural Benin, west Africa. *Dementia and Geriatric Cognitive Disorders*, *27*(1), 34-41. doi:10.1159/000188661

Guerchet, M., M'belesso, P., Mouanga, A. M., Bandzouzi, B., Tabo, A., Houinato, D. S. et al. (2010). Prevalence of dementia in elderly living in two cities of Central Africa: the EDAC survey. *Dementia and Geriatric Cognitive Disorders*, *30*(3), 261-268. doi:10.1159/000320247

Gunstad, J., Paul, R. H., Brickman, A. M., Cohen, R. A., Arns, M., Roe, D. et al. (2006). Patterns of cognitive performance in middle-aged and older adults: A cluster analytic examination. *Journal of Geriatric Psychiatry and Neurology, 19*(2), 59-64.

Gureje, O., Ogunniyi, A., Baiyewu, O., Price, B., Unverzagt, F. W., Evans, R. M. et al. (2006). APOE epsilon4 is not associated with Alzheimer's disease in elderly Nigerians. *Annals of Neurology*, *59*(1), 182-185. doi:10.1002/ana.20694

Gureje, O., Ogunniyi, A., Kola, L., & Abiona, T. (2011). Incidence of and risk factors for dementia in the Ibadan study of aging. *Journal of the American Geriatrics Society, 59*(5), 869-874. doi:10.1111/j.1532-5415.2011.03374.x

Gurvits, T. V., Shenton, M. E., Hokama, H., Ohta, H., Lasko, N. B., Gilbertson, M. W. et al. (1996). Magnetic resonance imaging study of hippocampal volume in chronic, combat-related posttraumatic stress disorder. *Biological Psychiatry, 40*(11), 1091-1099. doi:10.1016/S0006-3223(96)00229-6

Haass, C., Kaether, C., Thinakaran, G., & Sisodia, S. (2012). Trafficking and proteolytic processing of APP. *Cold Spring Harbor Perspectives in Medicine, 2*(5), a006270. doi:10.1101/cshperspect.a006270

Hakansson, K., Rovio, S., Helkala, E. L., Vilska, A. R., Winblad, B., Soininen, H. et al. (2009). Association between mid-life marital status and cognitive function in later life: population based cohort study. *British Medical Journal, 339*, b2462.

Hall, C. B., Derby, C., LeValley, A., Katz, M. J., Verghese, J., & Lipton, R. B. (2007). Education delays accelerated decline on a memory test in persons who develop dementia. *Neurology*, *69*(17), 1657-1664. doi:10.1212/01.wnl.0000278163.82636.30

Hall, K., Murrell, J., Ogunniyi, A., Deeg, M., Baiyewu, O., Gao, S. et al. (2006). Cholesterol, APOE genotype, and Alzheimer disease: an epidemiologic study of Nigerian Yoruba. *Neurology*, *66*(2), 223-227. doi:10.1212/01.wnl.0000194507.39504.17

Hamad, R., Fernald, L. C., Karlan, D. S., & Zinman, J. (2008). Social and economic correlates of depressive symptoms and perceived stress in South African adults. *Journal of Epidemioogy and Community Health, 62*(6), 538-544. doi:62/6/538

Hamber, B. & Lewis, S. (1997). *An overview of the consequences of violence and trauma in South Africa*. CT: Centre for the Study of Violence and Reconciliation.

Han, X., Jovicich, J., Salat, D., van der Kouwe, A., Quinn, B., Czanner, S. et al. (2006). Reliability of MRI-derived measurements of human cerebral cortical thickness: the effects of field strength, scanner upgrade and manufacturer. *NeuroImage, 32*(1), 180-194.

Hankey G. J. & Wardlaw, J. M. (2008). *Clinical Neurology.* London: Manson Publishing Ltd.

Hansen, R. A., Gartlehner, G., Webb, A. P., Morgan, L. C., Moore, C. G., & Jonas, D. E. (2008). Efficacy and safety of donepezil, galantamine, and rivastigmine for the treatment of Alzheimer's disease: a systematic review and meta-analysis. *Clinical Interventions in Aging*, *3*(2), 211-225.

Harasty, J. A., Halliday, G. M., Kril, J. J., & Code, C. (1999). Specific temporoparietal gyral atrophy reflects the pattern of language dissolution in Alzheimer's disease. *Brain, 122 (Pt 4)*675-686.

Hardy, J. & Selkoe, D. J. (2002). The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science, 297*(5580), 353-356. doi:10.1126/science.1072994

Hashimoto, M., Yasuda, M., Tanimukai, S., Matsui, M., Hirono, N., Kazui, H. et al. (2001). Apolipoprotein E epsilon 4 and the pattern of regional brain atrophy in Alzheimer's disease. *Neurology*, *57*(8), 1461-1466.

Hebert, L. E., Weuve, J., Scherr, P. A., & Evans, D. A. (2013). Alzheimer disease in the United States (2010-2050) estimated using the 2010 census. *Neurology*, *80*(19), 1778-1783. doi:10.1212/WNL.0b013e31828726f5

Heckmann, J. M., Low, W. C., de, V. C., Rutherfoord, S., Vorster, A., Rao, H. et al. (2004). Novel presenilin 1 mutation with profound neurofibrillary pathology in an indigenous Southern African family with early-onset Alzheimer's disease. *Brain*, *127*(Pt 1), 133-142. doi:10.1093/brain/awh009

Helzner, E. P., Luchsinger, J. A., Scarmeas, N., Cosentino, S., Brickman, A. M., Glymour, M. M. et al. (2009). Contribution of vascular risk factors to the progression in Alzheimer disease. *Archives of Neurology*, *66*(3), 343-348. doi:10.1001/archneur.66.3.343

Henderson, A. S., Easteal, S., Jorm, A. F., Mackinnon, A. J., Korten, A. E., Christensen, H. et al. (1995). Apolipoprotein E allele epsilon 4, dementia, and cognitive decline in a population sample. *Lancet*, *346*(8987), 1387-1390.

Hendrie, H. C., Osuntokun, B. O., Hall, K. S., Ogunniyi, A. O., Hui, S. L., Unverzagt, F. W. et al. (1995). Prevalence of Alzheimer's disease and dementia in two communities: Nigerian Africans and African Americans. *American Journal of Psychiatry*, *152*(10), 1485-1492.

Henry, J. P. (1992). Biological basis of the stress response. *Integrative Physiological and Behavioral Science*, *27*(1), 66-83.

Herbert, J. (2013). Cortisol and depression: three questions for psychiatry. *Psychological Medicine*, *43*(3), 449-469. doi:10.1017/S0033291712000955

Herman, A. A., Stein, D. J., Seedat, S., Heeringa, S. G., Moomal, H., & Williams, D. R. (2009). The South African Stress and Health (SASH) study: 12-month and lifetime prevalence of common mental disorders. *South African Medical Journal*, *99*(5 Pt 2), 339-344.

Het, S., Schoofs, D., Rohleder, N., & Wolf, O. T. (2012). Stress-induced cortisol level elevations are associated with reduced negative affect after stress: indications for a mood-buffering cortisol effect. *Psychosomatic Medicine, 74*(1), 23-32.

Hixson, J. E. & Vernier, D. T. (1990). Restriction isotyping of human apolipoprotein E by gene amplification and cleavage with HhaI. *Journal of Lipid Research, 31*(3), 545-548.

Hobson, P. & Meara, J. (1999). The detection of dementia and cognitive impairment in a community population of elderly people with Parkinson's disease by use of the CAMCOG neuropsychological test. *Age and Ageing, 28*(1), 39-43.

Hofstede G. & Hofstede, G. J. (2005). *Cultures and organizations: Software of the mind*. New York: McGraw-Hill.

Holland, D., Desikan, R. S., Dale, A. M., & McEvoy, L. K. (2013). Higher Rates of Decline for Women and Apolipoprotein E4 Carriers. *American Journal of Neuroradiology*, doi:10.3174/ajnr.A3601

Holtzman, D. M. (2009). A surrogate marker for Abeta42 production in the CNS. *EMBO Molecular Medicine*, *1*(4), 195-197. doi:10.1002/emmm.200900030

Holtzman, D. M., Herz, J., & Bu, G. (2012). Apolipoprotein E and apolipoprotein E receptors: normal biology and roles in Alzheimer disease. *Cold Spring Harbor Perspectives in Medicine*, *2*(3), a006312. doi:10.1101/cshperspect.a006312

Hua, X., Leow, A. D., Parikshak, N., Lee, S., Chiang, M. C., Toga, A. W. et al. (2008). Tensor-based morphometry as a neuroimaging biomarker for Alzheimer's disease: an MRI study of 676 AD, MCI, and normal subjects. *Neuroimage*, *43*(3), 458-469. doi:10.1016/j.neuroimage.2008.07.013

Huppert, F. A., Brayne, C., Gill, C., Paykel, E. S., & Beardsall, L. (1995). CAMCOG--a concise neuropsychological test to assist dementia diagnosis: socio-demographic determinants in an elderly population sample. *British Journal of Clinical Psychology*, *34*, 529-541.

Igbinomwanhia, N. G., James, B. O., & Omoaregba, J. O. (2013). The attitudes of clergy in Benin City, Nigeria towards persons with mental illness. *African Journal of Psychiatry (Johannesberg), 16*(3), 196-200. doi:10.4314/ajpsy.v16i3.26

Iqbal, K. & Grundke-Iqbal, I. (2006). Discoveries of tau, abnormally hyperphosphorylated tau and others of neurofibrillary degeneration: a personal historical perspective. *Journal of Alzheimer's Disease*, *9*(3 Suppl), 219-242.

Jack, C. R., Jr., Petersen, R. C., Xu, Y. C., Waring, S. C., O'Brien, P. C., Tangalos, E. G. et al. (1997). Medial temporal atrophy on MRI in normal aging and very mild Alzheimer's disease. *Neurology*, *49*(3), 786-794.

Jellinger, K. A., Paulus, W., Wrocklage, C., & Litvan, I. (2001). Traumatic brain injury as a risk factor for Alzheimer disease. Comparison of two retrospective autopsy cohorts with evaluation of ApoE genotype. *BMC Neurology*, *1*3.

Jelsma, J., Mkoka, S., Amosun, L., & Nieuwveldt, J. (2004). The reliability and validity of the Xhosa version of the EQ-5D. *Disability and Rehabilitation, 26*(2), 103-108. doi:10.1080/09638280310001629705

Jenkins, R., Fox, N. C., Rossor, A. M., Harvey, R. J., & Rossor, M. N. (2000). Intracranial volume and Alzheimer disease: evidence against the cerebral reserve hypothesis. *Archives of Neurology, 57*(2), 220-224.

Jenni, M. A. & Wollersheim, J. P. (1979). Cognitive therapy, stress management training, and the Type A behaviour pattern. *Cognitive Therapy and Research, 3*(1), 61-73.

Johansson, L., Guo, X., Waern, M., Ostling, S., Gustafson, D., Bengtsson, C. et al. (2010). Midlife psychological stress and risk of dementia: a 35-year longitudinal population study. *Brain, 133*(Pt 8), 2217-2224. doi:10.1093/brain/awq116

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. doi:10.1001/archneurol.2009.158

Jonker, C., Schmand, B., Lindeboom, J., Havekes, L. M., & Launer, L. J. (1998). Association between apolipoprotein E epsilon4 and the rate of cognitive decline in community-dwelling elderly individuals with and without dementia. *Archives of Neurology, 55*(8), 1065-1069.

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

Joska, J. A., Combrinck, M., Valcour, V. G., Hoare, J., Leisegang, F., Mahne, A. C. et al. (2010). Association between apolipoprotein E4 genotype and human immunodeficiency virus-associated dementia in younger adults starting antiretroviral therapy in South Africa. *Journal of Neurovirology, 16*(5), 377-383. doi:10.3109/13550284.2010.513365

Joubert, J. & Bradshaw, D. (2006). *Population ageing and health challenges in South Africa*. Chapter 15. (pp. 1-16).

Juster, R. P., McEwen, B. S., & Lupien, S. J. (2010). Allostatic load biomarkers of chronic stress and impact on health and cognition. *Neuroscience & Biobehavioral Reviews, 35*(1), 2-16. doi:10.1016/j.neubiorev.2009.10.002

Kabir, M., Iliyasu, Z., Abubakar, I. S., & Aliyu, M. H. (2004). Perception and beliefs about mental illness among adults in Karfi village, northern Nigeria. *BMC International Health and Human Rights, 4*(1), 3. doi:10.1186/1472-698X-4-3

Kalaria, R. N., Maestre, G. E., Arizaga, R., Friedland, R. P., Galasko, D., Hall, K. et al. (2008). Alzheimer's disease and vascular dementia in developing countries: prevalence, management, and risk factors. *Lancet Neurology, 7*(9), 812-826. doi:10.1016/S1474-4422(08)70169-8

Kalmijn, S., Janssen, J. A., Pols, H. A., Lamberts, S. W., & Breteler, M. M. (2000). A prospective study on circulating insulin-like growth factor I (IGF-I), IGF-

binding proteins, and cognitive function in the elderly. *Journal of Clinical Endocrinology & Metabolism*, *85*(12), 4551-4555.

Kalmijn, S., Launer, L. J., Lindemans, J., Bots, M. L., Hofman, A., & Breteler, M. M. (1999). Total homocysteine and cognitive decline in a community-based sample of elderly subjects: the Rotterdam Study. *American Journal of Epidemiology*, *150*(3), 283-289.

Kalula, S. Z., Ferreira, M., Thomas, K. G., de, V. L., Joska, J. A., & Geffen, L. N. (2010). Profile and management of patients at a memory clinic. *South African Medical Journal*, *100*(7), 449-451.

Kang, J. E., Cirrito, J. R., Dong, H., Csernansky, J. G., & Holtzman, D. M. (2007). Acute stress increases interstitial fluid amyloid-beta via corticotropin-releasing factor and neuronal activity. *Proceedings of the National Academy of Sciences of the United States of America*, *104*(25), 10673-10678. doi:10.1073/pnas.0700148104

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

Karran, E., Mercken, M., & De, S. B. (2011). The amyloid cascade hypothesis for Alzheimer's disease: an appraisal for the development of therapeutics. *Nature Reviews Drug Discovery*, *10*(9), 698-712. doi:10.1038/nrd3505 [doi]

Katzman, R. (1989). Alzheimer's disease is a degenerative disorder. *Neurobiology of Aging*, *10*(5), 581-582.

Kawas, C., Gray, S., Brookmeyer, R., Fozard, J., & Zonderman, A. (2000). Age-specific incidence rates of Alzheimer's disease: the Baltimore Longitudinal Study of Aging. *Neurology*, *54*(11), 2072-2077.

Kemeny, M. E. (2013). Tjhe psychobiology of stress. *Current Directions in Psychological Science*, *12*124-129. doi:10.1111/1467-8721.01246

Kemppainen, N. M., Aalto, S., Karrasch, M., Nagren, K., Savisto, N., Oikonen, V. et al. (2008). Cognitive reserve hypothesis: Pittsburgh Compound B and fluorodeoxyglucose positron emission tomography in relation to education in mild Alzheimer's disease. *Annals of Neurology*, *63*(1), 112-118. doi:10.1002/ana.21212

Kim, J. W., Lee, H. K., & Lee, K. (2013). Influence of temperament and character on resilience. *Comprehensive Psychiatry*, doi:10.1016/j.comppsych.2013.05.005

Kinsella, K. & Ferreira, M. (1997). *Ageing trends: South Africa*. U.S. Dept. of Commerce, Economics and Statistics Administration, Bureau of the Census.

Knoops, A. J., Gerritsen, L., van der Graaf, Y., Mali, W. P., & Geerlings, M. I. (2012). Loss of entorhinal cortex and hippocampal volumes compared to whole brain volume in normal aging: the SMART-Medea study. *Psychiatry Research*, *203*(1), 31-37. doi:10.1016/j.pscychresns.2011.12.002

Kowalczyk, A., McDonald, S., Cranney, J., & McMahon, M. (2001). Cognitive Flexibility in the Normal Elderly and in Persons with Dementia as Measured by the Written and Oral Trail Making Tests. *Brain Impairment, 2*(1), 11-21. doi:http://dx.doi.org/10.1375/brim.2.1.11

Koyama, A., Okereke, O. I., Yang, T., Blacker, D., Selkoe, D. J., & Grodstein, F. (2012). Plasma amyloid-beta as a predictor of dementia and cognitive decline: a systematic review and meta-analysis. *Archives of Neurology, 69*(7), 824-831. doi:10.1001/archneurol.2011.1841

Krasuski, J. S., Alexander, G. E., Horwitz, B., Daly, E. M., Murphy, D. G., Rapoport, S. I. et al. (1998). Volumes of medial temporal lobe structures in patients with Alzheimer's disease and mild cognitive impairment (and in healthy controls). *Biological Psychiatry, 43*(1), 60-68.

Krause, N. (1999). Mental disorders in late life: Exploring the influence of stress and socioeconomic status. In C. S. Aneshensel & J. C. Phelan, (Eds.), *Handbook of the Sociology of Mental Health* (183-208) New York: Plenum Press.

Krause, N. (2005). Exploring age differences in the stress-buffering function of social support. *Psychology and Aging, 20*(4), 714-717. doi:10.1037/0882-7974.20.4.714

Kreek, M. J., Nielsen, D. A., Butelman, E. R., & LaForge, K. S. (2005). Genetic influences on impulsivity, risk taking, stress responsivity and vulnerability to drug abuse and addiction. *Nature Neuroscience, 8*(11), 1450-1457. doi:10.1038/nn1583

Kubzansky, L. D., Berkman, L. F., Glass, T. A., & Seeman, T. E. (1998). Is educational attainment associated with shared determinants of health in the elderly? Findings from the MacArthur Studies of Successful Aging. *Psychosomatic Medicine, 60*(5), 578-585.

Kudielka, B. M., Hellhammer, J., Hellhammer, D. H., Wolf, O. T., Pirke, K. M., Varadi, E. et al. (1998). Sex differences in endocrine and psychological responses to psychosocial stress in healthy elderly subjects and the impact of a 2-week dehydroepiandrosterone treatment. *The Journal of Clinical Endocrinology and Metabolism, 83*(5), 1756-1761.

Kudielka, B. M. & Kirschbaum, C. (2005). Sex differences in HPA axis responses to stress: a review. *Biological Psychology, 69*(1), 113-132. doi:10.1016/j.biopsycho.2004.11.009

Kulstad, J. J., McMillan, P. J., Leverenz, J. B., Cook, D. G., Green, P. S., Peskind, E. R. et al. (2005). Effects of chronic glucocorticoid administration on insulin-degrading enzyme and amyloid-beta peptide in the aged macaque. *Journal of Neuropathology & Experimental Neurology, 64*(2), 139-146.

Kyle, J., Fox, H. C., & Whalley, L. J. (2010). Caffeine, cognition, and socioeconomic status. *Journal of Alzheimers Disease, 20 Suppl 1(*S1), 51-S159. doi:484200673UG17400 [pii];10.3233/JAD-2010-1409 [doi]

Lachize, S., Apostolakis, E. M., van der Laan, S., Tijssen, A. M., Xu, J., de Kloet, E. R. et al. (2009). Steroid receptor coactivator-1 is necessary for regulation of corticotropin-releasing hormone by chronic stress and glucocorticoids. *Proceedings of the National Academy of Sciences, 106*(19), 8038-8042. doi:10.1073/pnas.0812062106

Lane, R. M. & Farlow, M. R. (2005). Lipid homeostasis and apolipoprotein E in the development and progression of Alzheimer's disease. *Journal of Lipid Research, 46*(5), 949-968. doi:10.1194/jlr.M400486-JLR200

Larsson, C. A., Gullberg, B., Rastam, L., & Lindblad, U. (2009). Salivary cortisol differs with age and sex and shows inverse associations with WHR in Swedish women: a cross-sectional study. *BMC Endocrine Disorders, 9*16. doi:10.1186/1472-6823-9-16

Lawn, S. D., Harries, A. D., Anglaret, X., Myer, L., & Wood, R. (2008). Early mortality among adults accessing antiretroviral treatment programmes in sub-Saharan Africa. *AIDS, 22*(15), 1897-1908. doi:10.1097/QAD.0b013e32830007cd

Lee, B. K., Glass, T. A., McAtee, M. J., Wand, G. S., Bandeen-Roche, K., Bolla, K. I. et al. (2007). Associations of salivary cortisol with cognitive function in the Baltimore memory study. *Archives of General Psychiatry, 64*(7), 810-818.

Lee, B. K., Glass, T. A., Wand, G. S., McAtee, M. J., Bandeen-Roche, K., Bolla, K. I. et al. (2008). Apolipoprotein e genotype, cortisol, and cognitive function in community-dwelling older adults. *American Journal of Psychiatry, 165*(11), 1456-1464. doi:10.1176/appi.ajp.2008.07091532

Lee, T., Jarome, T., Li, S. J., Kim, J. J., & Helmstetter, F. J. (2009). Chronic stress selectively reduces hippocampal volume in rats: a longitudinal magnetic resonance imaging study. *NeuroReport, 20*(17), 1554-1558. doi:10.1097/WNR.0b013e328332bb09

Leeds, L., Meara, R. J., Woods, R., & Hobson, J. P. (2001). A comparison of the new executive functioning domains of the CAMCOG-R with existing tests of executive function in elderly stroke survivors. *Age and Ageing, 30*(3), 251-254.

Legido-Quigley, H. (2003). The South African old age pension: Exploring the role of poverty alleviation in households affected by HIV/AIDS. *International Social Security Information.* http://www.eldis.org/go/home&id=13604&type=Document#.UptRbMRQKm6

Lenger, V., de Viliers, C., & Louw, S. J. (1996). Informant questionnaires as screening measures to detect dementia. A pilot study in the South African context. *South African Medical Journal, 86*(6 Suppl), 737-741.

Letenneur, L., Launer, L. J., Andersen, K., Dewey, M. E., Ott, A., Copeland, J. R. et al. (2000). Education and the risk for Alzheimer's disease: sex makes a difference. EURODEM pooled analyses. EURODEM Incidence Research Group. *American Journal of Epidemiology, 151*(11), 1064-1071.

Levey, A., Lah, J., Goldstein, F., Steenland, K., & Bliwise, D. (2006). Mild cognitive impairment: an opportunity to identify patients at high risk for progression to Alzheimer's disease. *Clinical Therapeutics, 28*(7), 991-1001. doi:10.1016/j.clinthera.2006.07.006

Lezak M. D., Howieson, D. B., & Loring, D. W. (2004). *Neuropsychological Assessment.* New York: Oxford University Press.

Lindsay, J., Laurin, D., Verreault, R., Hebert, R., Helliwell, B., Hill, G. B. et al. (2002). Risk factors for Alzheimer's disease: a prospective analysis from the Canadian Study of Health and Aging. *American Journal of Epidemiology, 156*(5), 445-453.

Liu, C. C., Kanekiyo, T., Xu, H., & Bu, G. (2013). Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. *Nature Reviews Neurology, 9*(2), 106-118. doi:10.1038/nrneurol.2012.263

Luchsinger, J. A., Reitz, C., Honig, L. S., Tang, M. X., Shea, S., & Mayeux, R. (2005). Aggregation of vascular risk factors and risk of incident Alzheimer disease. *Neurology, 65*(4), 545-551. doi:10.1212/01.wnl.0000172914.08967.dc

Luchsinger, J. A., Tang, M. X., Shea, S., & Mayeux, R. (2004). Hyperinsulinemia and risk of Alzheimer disease. *Neurology, 63*(7), 1187-1192.

Lui, J. K., Laws, S. M., Li, Q. X., Villemagne, V. L., Ames, D., Brown, B. et al. (2010). Plasma amyloid-beta as a biomarker in Alzheimer's disease: the AIBL study of aging. *Journal of Alzheimers Disease, 20*(4), 1233-1242. doi:10.3233/JAD-2010-090249

Luine, V., Villegas, M., Martinez, C., & McEwen, B. S. (1994). Repeated stress causes reversible impairments of spatial memory performance. *Brain Research, 639*(1), 167-170.

Lupien, S., Lecours, A. R., Lussier, I., Schwartz, G., Nair, N. P., & Meaney, M. J. (1994). Basal cortisol levels and cognitive deficits in human aging. *The Journal of Neuroscience, 14*(5 Pt 1), 2893-2903.

Lupien, S. J., de, L. M., de, S. S., Convit, A., Tarshish, C., Nair, N. P. et al. (1998). Cortisol levels during human aging predict hippocampal atrophy and memory deficits. *Nature Neuroscience, 1*(1), 69-73. doi:10.1038/271

Lupien, S. J., Gaudreau, S., Tchiteya, B. M., Maheu, F., Sharma, S., Nair, N. P. et al. (1997a). Stress-induced declarative memory impairment in healthy elderly subjects: relationship to cortisol reactivity. *The Journal of Clinical Endocrinology and Metabolism, 82*(7), 2070-2075.

Lupien, S. J. & McEwen, B. S. (1997b). The acute effects of corticosteroids on cognition: integration of animal and human model studies. *Brain Research Reviews, 24*(1), 1-27.

Lupien, S. J., McEwen, B. S., Gunnar, M. R., & Heim, C. (2009). Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nature Reviews Neuroscience*, *10*(6), 434-445. doi:10.1038/nrn2639

MacIntyre, P. D. & Gardner, R. C. (1994). Subtle Effects of Language Anxiety on Cognitive Processing in the Second Language. *Language Learning*, *44*283-305. doi:10.1111/j.1467-1770.1994.tb01103.x

MacLullich, A. M., Deary, I. J., Starr, J. M., Ferguson, K. J., Wardlaw, J. M., & Seckl, J. R. (2005). Plasma cortisol levels, brain volumes and cognition in healthy elderly men. *Psychoneuroendocrinology*, *30*(5), 505-515. doi:10.1016/j.psyneuen.2004.12.005

Magarinos, A. M., McEwen, B. S., Flugge, G., & Fuchs, E. (1996). Chronic psychosocial stress causes apical dendritic atrophy of hippocampal CA3 pyramidal neurons in subordinate tree shrews. *The Journal of Neuroscience*, *16*(10), 3534-3540.

Mahley, R. W., Weisgraber, K. H., & Huang, Y. (2009). Apolipoprotein E: structure determines function, from atherosclerosis to Alzheimer's disease to AIDS. *Journal of Lipid Research*, *50 Suppl*, 183-S188. doi:10.1194/jlr.R800069-JLR200

Makanjuola, A. B., Adelekan, M. L., & Morakinyo, O. (2000). Current status of traditional mental health practice in Ilorin Emirate Council area, Kwara State, Nigeria. *West African Journal of Medicine*, *19*(1), 43-49.

Malecki, C. K. & Demaray, M. K. (2006). Social support as a buffer in the relationship between socioeconomic status and academic performance. *School Psychology Quarterly*, *21*(4), 375-395. doi:10.1037/h0084129

Maletic, V., Robinson, M., Oakes, T., Iyengar, S., Ball, S. G., & Russell, J. (2007). Neurobiology of depression: an integrated view of key findings. *International Journal of Clinical Practice*, *61*(12), 2030-2040. doi:10.1111/j.1742-1241.2007.01602.x

Manly, J. J. (2005). Advantages and disadvantages of separate norms for African Americans. *Clinical Neuropsychology*, *19*(2), 270-275. doi:10.1080/13854040590945346

Manly, J. J. (2008). Critical issues in cultural neuropsychology: profit from diversity. *Neuropsychology Review*, *18*(3), 179-183. doi:10.1007/s11065-008-9068-8

Manly, J. J., Jacobs, D. M., Sano, M., Bell, K., Merchant, C. A., Small, S. A. et al. (1998). Cognitive test performance among nondemented elderly African Americans and whites. *Neurology*, *50*(5), 1238-1245.

Manly, J. 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*(3), 341-348.

Mann, C. J. (2003). Observational research methods. Research design II: cohort, cross sectional, and case-control studies. *Emergency Medicine Journal*, *20*(1), 54-60.

Martins, C. A., Oulhaj, A., de Jager, C. A., & Williams, J. H. (2005). APOE alleles predict the rate of cognitive decline in Alzheimer disease: a nonlinear model. *Neurology*, *65*(12), 1888-1893. doi:10.1212/01.wnl.0000188871.74093.12

Masliah, E., Rockenstein, E., Veinbergs, I., Sagara, Y., Mallory, M., Hashimoto, M. et al. (2001). beta-amyloid peptides enhance alpha-synuclein accumulation and neuronal deficits in a transgenic mouse model linking Alzheimer's disease and Parkinson's disease. *Proceedings of the National Academy of Sciences of the United States of America*, *98*(21), 12245-12250. doi:10.1073/pnas.211412398

Mathuranath, P. S., George, A., Ranjith, N., Justus, S., Kumar, M. S., Menon, R. et al. (2012). Incidence of Alzheimer's disease in India: a 10 years follow-up study. *Neurology India*, *60*(6), 625-630. doi:10.4103/0028-3886.105198

Matsuda, H. (2007). Role of neuroimaging in Alzheimer's disease, with emphasis on brain perfusion SPECT. *Journal of Nuclear Medicine*, *48*(8), 1289-1300. doi:10.2967/jnumed.106.037218

Matud, M. P. (2004). Gender differences in stress and coping styles. *Personality and Individual Differences*, *37*, 1401-1415.

Mayeux, R. (2003). Apolipoprotein E, Alzheimer disease, and African Americans. *Archives of Neurology*, *60*(2), 161-163.

Mayeux, R., Honig, L. S., Tang, M. X., Manly, J., Stern, Y., Schupf, N. et al. (2003). Plasma A[beta]40 and A[beta]42 and Alzheimer's disease: relation to age, mortality, and risk. *Neurology*, *61*(9), 1185-1190.

McDonald, R. J. (2002). Multiple combinations of co-factors produce variants of age-related cognitive decline: a theory. *Canadian Journal of Experimental Psychology*, *56*(3), 221-239.

McEvoy, L. K. & Brewer, J. B. (2010). Quantitative structural MRI for early detection of Alzheimer's disease. *Expert Review of Neurotherapeutics*, *10*(11), 1675-1688. doi:10.1586/ern.10.162

McEwen, B. S. (1998). Stress, adaptation, and disease. Allostasis and allostatic load. *Annals of the New York Academy of Sciences*, *840*33-44.

McEwen, B. S. (2004a). Protection and damage from acute and chronic stress: allostasis and allostatic overload and relevance to the pathophysiology of psychiatric disorders. *Annals of the New York Academy of Sciences*, *1032*1-7. doi:1032/1/1 [pii];10.1196/annals.1314.001

McEwen, B. S. (2004b). Structural plasticity of the adult brain: how animal models help us understand brain changes in depression and systemic disorders related to depression. *Dialogues in Clinical Neuroscience*, *6*(2), 119-133.

McEwen, B. S. (2005). Stressed or stressed out: what is the difference? *Journal of & Psychiatry Neuroscience, 30*(5), 315-318.

McEwen, B. S. (2007). Physiology and neurobiology of stress and adaptation: central role of the brain. *Physiological Reviews, 87*(3), 873-904. doi:10.1152/physrev.00041.2006

McEwen, B. S. (2008). Understanding the potency of stressful early life experiences on brain and body function. *Metabolism, 57 (Suppl), 2*S11-S15. doi:10.1016/j.metabol.2008.07.006

McEwen, B. S. & Sapolsky, R. M. (1995). Stress and cognitive function. *Current Opinion in Neurobiology, 5*(2), 205-216.

McEwen, B. S. & Seeman, T. (1999). Protective and damaging effects of mediators of stress. Elaborating and testing the concepts of allostasis and allostatic load. *Annals of the New York Academy of Sciences, 896*30-47.

McEwen, B. S. & Stellar, E. (1993). Stress and the individual. Mechanisms leading to disease. *Archives of Internal Medicine, 153*(18), 2093-2101.

McEwen, B. S., Weiss, J. M., & Schwartz, L. S. (1968). Selective retention of corticosterone by limbic structures in rat brain. *Nature, 220*(5170), 911-912.

McEwen, B. S. & Wingfield, J. C. (2010). What is in a name? Integrating homeostasis, allostasis and stress. *Hormones and Behavior, 57*(2), 105-111. doi:10.1016/j.yhbeh.2009.09.011

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., & Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology, 34*(7), 939-944.

Mehta, P. D., Pirttila, T., Mehta, S. P., Sersen, E. A., Aisen, P. S., & Wisniewski, H. M. (2000). Plasma and cerebrospinal fluid levels of amyloid beta proteins 1-40 and 1-42 in Alzheimer disease. *Archives of Neurology, 57*(1), 100-105.

Meinz, E. J. & Salthouse, T. A. (1998). The effects of age and experience on memory for visually presented music. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences, 53*(1), 60-69.

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. doi:10.1371/journal.pone.0038268

Miech, R. A. & Hauser, R. M. (2001). Socioeconomic status and health at midlife. A comparison of educational attainment with occupation-based indicators. *Annals of Epidemiology, 11*(2), 75-84.

Miller, G. E., Chen, E., & Zhou, E. S. (2007). If it goes up, must it come down? Chronic stress and the hypothalamic-pituitary-adrenocortical axis in humans. *Psychological Bulletin, 133*(1), 25-45. doi:10.1037/0033-2909.133.1.25

Minati, L., Edginton, T., Bruzzone, M. G., & Giaccone, G. (2009). Current concepts in Alzheimer's disease: a multidisciplinary review. *American Journal of Alzheimer's Disease and Other Dementias*, *24*(2), 95-121. doi:10.1177/1533317508328602

Moghekar, A., Kraut, M., Elkins, W., Troncoso, J., Zonderman, A. B., Resnick, S. M. et al. (2012). Cerebral white matter disease is associated with Alzheimer pathology in a prospective cohort. *Alzheimer's & Dementia*, *8*(5 Suppl), S71-S77. doi:10.1016/j.jalz.2012.04.006

Morilak, D. A., Barrera, G., Echevarria, D. J., Garcia, A. S., Hernandez, A., Ma, S. et al. (2005). Role of brain norepinephrine in the behavioral response to stress. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *29*(8), 1214-1224. doi:10.1016/j.pnpbp.2005.08.007

Morris, J. C. (2006). Mild cognitive impairment is early-stage Alzheimer disease: time to revise diagnostic criteria. *Archives of Neurology*, *63*(1), 15-16. doi:10.1001/archneur.63.1.15

Morris, J. C. & Price, J. L. (2001). Pathologic correlates of nondemented aging, mild cognitive impairment, and early-stage Alzheimer's disease. *Journal of Molecular Neuroscience*, *17*(2), 101-118.

Morris, M. C., Rao, U., & Garber, J. (2012). Cortisol responses to psychosocial stress predict depression trajectories: social-evaluative threat and prior depressive episodes as moderators. *Journal of Affective Disorders*, *143*(1-3), 223-230. doi: 10.1016/j.jad.2012.05.059

Mortimer, J. A. (2012). The Nun Study: risk factors for pathology and clinical-pathologic correlations. *Current Alzheimer Research*, *9*(6), 621-627.

Muller, A. (2002). Education, income inequality, and mortality: a multiple regression analysis. *British Medical Journal*, *324*(7328), 23-25.

Muniz-Terrera, G., Matthews, F., Dening, T., Huppert, F. A., & Brayne, C. (2009). Education and trajectories of cognitive decline over 9 years in very old people: methods and risk analysis. *Age and Ageing*, *38*(3), 277-282. doi:10.1093/ageing/afp004

Murrell, J. R., Price, B., Lane, K. A., Baiyewu, O., Gureje, O., Ogunniyi, A. et al. (2006). Association of apolipoprotein E genotype and Alzheimer disease in African Americans. *Archives of Neurology*, *63*(3), 431-434. doi:10.1001/archneur.63.3.431

Musicco, M., Salamone, G., Caltagirone, C., Cravello, L., Fadda, L., Lupo, F. et al. (2010). Neuropsychological predictors of rapidly progressing patients with Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders*, *30*(3), 219-228. doi:10.1159/000319533

Muula, A. S. (2008). HIV infection and AIDS among young women in South Africa. *Croatian Medical Journal*, *49*(3), 423-435.

Nell V. (2000). *Cross-Cultural Neuropsychological Assessment: Theory and Practice.* Mahwah, NJ: Lawrence Erlbaum Associates.

Neupert, S. D., Almeida, D. M., Mroczek, D. K., & Spiro, A., III. (2006). Daily stressors and memory failures in a naturalistic setting: findings from the VA Normative Aging Study. *Psychology and Aging, 21*(2), 424-429. doi:10.1037/0882-7974.21.2.424

Ng, T. P., Feng, L., Niti, M., Kua, E. H., & Yap, K. B. (2008). Tea consumption and cognitive impairment and decline in older Chinese adults. *American Journal of Clinical Nutrition, 88*(1), 224-231.

NIH Research Portfolio Online Reporting Tools. (2012). National Institutes of Health Estimates of Funding for Various Research, Condition, and Disease Categories (RCDC) FY 2012.

Niti, M., Yap, K. B., Kua, E. H., & Ng, T. P. (2009). APOE-epsilon4, depressive symptoms, and cognitive decline in Chinese older adults: Singapore Longitudinal Aging Studies. *Journal of Gerontology. Series A: Biological Sciences and Medical Sciences, 64*(2), 306-311. doi:gln013

Notkola, I. L., Sulkava, R., Pekkanen, J., Erkinjuntti, T., Ehnholm, C., Kivinen, P. et al. (1998). Serum total cholesterol, apolipoprotein E epsilon 4 allele, and Alzheimer's disease. *Neuroepidemiology, 17*(1), 14-20.

O'Brien, J. T. (2007). Role of imaging techniques in the diagnosis of dementia. *British Journal of Radiology, 80, 2*S71-S77. doi:10.1259/bjr/33117326

O'Brien, J. T., Ames, D., Schweitzer, I., Mastwyk, M., & Colman, P. (1996). Enhanced adrenal sensitivity to adrenocorticotrophic hormone (ACTH) is evidence of HPA axis hyperactivity in Alzheimer's disease. *Psychological Medicine, 26*(1), 7-14.

O'Brien, J. T., Erkinjuntti, T., Reisberg, B., Roman, G., Sawada, T., Pantoni, L. et al. (2003). Vascular cognitive impairment. *Lancet Neurology, 2*(2), 89-98.

O'Bryant, S. E., Humphreys, J. D., Smith, G. E., Ivnik, R. J., Graff-Radford, N. R., Petersen, R. C. et al. (2008). Detecting dementia with the mini-mental state examination in highly educated individuals. *Archives of Neurology, 65*(7), 963-967. doi:10.1001/archneur.65.7.963

O'Dwyer, L., Lamberton, F., Matura, S., Tanner, C., Scheibe, M., Miller, J. et al. (2012). Reduced hippocampal volume in healthy young ApoE4 carriers: an MRI study. *PLoS.One., 7*(11), e48895. doi:10.1371/journal.pone.0048895

Ochayi, B. & Thacher, T. D. (2006). Risk factors for dementia in central Nigeria. *Aging & Mental Health, 10*(6), 616-620. doi:10.1080/13607860600736182

Ogunniyi, A., Hall, K. S., Baiyewu, O., Gureje, O., Unverzagt, F. W., Gao, S. et al. (2005). Caring for individuals with dementia: the Nigerian experience. *West African Journal of Medicine, 24*(3), 259-262.

Okazaki, S. & Sue, S. (2000). Implications of test revisions for assessment with Asian Americans. *Psychological Assessment, 12*(3), 272-280.

Okoye, U. O. & Asa, S. S. (2013). Caregiving and stress: Experience of people taking care of elderly relations in South-easten Nigeria. *Arts and Social Sciences Journal, 2011*.

Oria, R. B., Patrick, P. D., Zhang, H., Lorntz, B., de Castro Costa, C. M., Brito, G. A. et al. (2005). APOE4 protects the cognitive development in children with heavy diarrhea burdens in Northeast Brazil. *Pediatric Research, 57*(2), 310-316. doi:10.1203/01.PDR.0000148719.82468.CA

Ostrosky-Solis, F., Ramirez, M., & Ardila, A. (2004). Effects of culture and education on neuropsychological testing: a preliminary study with indigenous and nonindigenous population. *Applied Neuropsychology, 11*(4), 188-195. doi:10.1207/s15324826an1104_3

Osuntokun, B. O., Sahota, A., Ogunniyi, A. O., Gureje, O., Baiyewu, O., Adeyinka, A. et al. (1995). Lack of an association between apolipoprotein E epsilon 4 and Alzheimer's disease in elderly Nigerians. *Annals of Neurology, 38*(3), 463-465. doi:10.1002/ana.410380319

Otte, C., Hart, S., Neylan, T. C., Marmar, C. R., Yaffe, K., & Mohr, D. C. (2005). A meta-analysis of cortisol response to challenge in human aging: importance of gender. *Psychoneuroendocrinology, 30*(1), 80-91. doi:10.1016/j.psyneuen.2004.06.002

Packard, C. J., Westendorp, R. G., Stott, D. J., Caslake, M. J., Murray, H. M., Shepherd, J. et al. (2007). Association between apolipoprotein E4 and cognitive decline in elderly adults. *Journal of American Geriatrics Society, 55*(11), 1777-1785. doi:10.1111/j.1532-5415.2007.01415

Papazacharias, A. & Nardini, M. (2012). The relationship between depression and cognitive deficits. *Psychiatria Danubina, 24 Suppl(1),* S179-S182.

Park, D. C. & Reuter-Lorenz, P. (2009). The adaptive brain: aging and neurocognitive scaffolding. *Annual Review of Psychology*, 60, 173-196. doi:10.1146/annurev.psych.59.103006.093656

Parrish, P. & Linder-vanBerschot, J. A. (2010). Cultural dimensions of learning: addressing the challenges of multicultural instruction. *The International Review of Research in Open and Distance Learning, 11*(2).

Pavlik, V. N., Doody, R. S., Massman, P. J., & Chan, W. (2006). Influence of premorbid IQ and education on progression of Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders, 22*(4), 367-377. doi:10.1159/000095640

Peavy, G. M., Jacobson, M. W., Salmon, D. P., Gamst, A. C., Patterson, T. L., Goldman, S. et al. (2012). The influence of chronic stress on dementia-related diagnostic change in older adults. *Alzheimer Disease and Associated Disorders, 26*(3), 260-266. doi:10.1097/WAD.0b013e3182389a9c

Peavy, G. M., Lange, K. L., Salmon, D. P., Patterson, T. L., Goldman, S., Gamst, A. C. et al. (2007). The effects of prolonged stress and APOE genotype on memory and cortisol in older adults. *Biological Psychiatry, 62*(5), 472-478. doi:10.1016/j.biopsych.2007.03.013

Peavy, G. M., Salmon, D. P., Jacobson, M. W., Hervey, A., Gamst, A. C., Wolfson, T. et al. (2009). Effects of chronic stress on memory decline in cognitively normal and mildly impaired older adults. *American Journal of Psychiatry, 166*(12), 1384-1391. doi:10.1176/appi.ajp.2009.09040461

Pennanen, C., Kivipelto, M., Tuomainen, S., Hartikainen, P., Hanninen, T., Laakso, M. P. et al. (2004). Hippocampus and entorhinal cortex in mild cognitive impairment and early AD. *Neurobiology of Aging, 25*(3), 303-310. doi:10.1016/S0197-4580(03)00084-8

Perry, B. D. & Pollard, R. (1998). Homeostasis, stress, trauma, and adaptation. A neurodevelopmental view of childhood trauma. *Child & Adolescent Psychiatric Clinics of North America, 7*(1), 33-51.

Perry, G., Zhu, X., Smith, M. A., Sorensen, A., & Avila, J. (2013). Preface. Alzheimer's disease: advances for a new century. *Journal of Alzheimer's Disease, 33 Suppl (1),* S1.

Peters, J. L., Weisskopf, M. G., Spiro, A., III, Schwartz, J., Sparrow, D., Nie, H. et al. (2010). Interaction of stress, lead burden, and age on cognition in older men: the VA Normative Aging Study. *Environmental Health Perspectives, 118*(4), 505-510. doi:10.1289/ehp.0901115

Peters, R., Poulter, R., Warner, J., Beckett, N., Burch, L., & Bulpitt, C. (2008). Smoking, dementia and cognitive decline in the elderly, a systematic review. *BMC Geriatrics, 8*36. doi:10.1186/1471-2318-8-36

Petersen, R. C. (2004). Mild cognitive impairment as a diagnostic entity. *Journal of Internal Medicine, 256*(3), 183-194. doi:10.1111/j.1365-2796.2004.01388.x

Petersen, R. C. (2011). Clinical practice. Mild cognitive impairment. *The New England Journal of Medicine, 364*(23), 2227-2234. doi:10.1056/NEJMcp0910237

Petersen, R. C., Stevens, J. C., Ganguli, M., Tangalos, E. G., Cummings, J. L., & DeKosky, S. T. (2001). Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology, 56*(9), 1133-1142.

Petot, G. J., Traore, F., Debanne, S. M., Lerner, A. J., Smyth, K. A., & Friedland, R. P. (2003). Interactions of apolipoprotein E genotype and dietary fat intake of healthy older persons during mid-adult life. *Metabolism, 52*(3), 279-281. doi:10.1053/meta.2003.50066

Petrella, J. R., Coleman, R. E., & Doraiswamy, P. M. (2003). Neuroimaging and early diagnosis of Alzheimer disease: a look to the future. *Radiology, 226*(2), 315-336.

Petros, N., Opacka-Juffry, J., & Huber, J. H. (2013). Psychometric and neurobiological assessment of resilience in a non-clinical sample of adults. *Psychoneuroendocrinology*, doi:10.1016/j.psyneuen.2013.03.022

Petruzzello, S. J., Landers, D. M., Hatfield, B. D., Kubitz, K. A., & Salazar, W. (1991). A meta-analysis on the anxiety-reducing effects of acute and chronic exercise. Outcomes and mechanisms. *Sports Medicine, 11*(3), 143-182.

Phuc, L. P., Friedman, J. R., Schug, J., Brestelli, J. E., Parker, J. B., Bochkis, I. M. et al. (2005). Glucocorticoid receptor-dependent gene regulatory networks. *PLOS Genetics, 1*(2), e16. doi:10.1371/journal.pgen.0010016

Pievani, M., Galluzzi, S., Thompson, P. M., Rasser, P. E., Bonetti, M., & Frisoni, G. B. (2011). APOE4 is associated with greater atrophy of the hippocampal formation in Alzheimer's disease. *Neuroimage, 55*(3), 909-919. doi:10.1016/j.neuroimage.2010.12.081

Plassman, B. L., Williams, J. W., Jr., Burke, J. R., Holsinger, T., & Benjamin, S. (2010). Systematic review: factors associated with risk for and possible prevention of cognitive decline in later life. *Annals of Internal Medicine, 153*(3), 182-193. doi:10.1059/0003-4819-153-3-201008030-00258

Podewils, L. J., Guallar, E., Kuller, L. H., Fried, L. P., Lopez, O. L., Carlson, M. et al. (2005). Physical activity, APOE genotype, and dementia risk: findings from the Cardiovascular Health Cognition Study. *American Journal of Epidemiology, 161*(7), 639-651. doi:10.1093/aje/kwi092

Polk, D. E., Cohen, S., Doyle, W. J., Skoner, D. P., & Kirschbaum, C. (2005). State and trait affect as predictors of salivary cortisol in healthy adults. *Psychoneuroendocrinology, 30*(3), 261-272. doi:10.1016/j.psyneuen.2004.08.004

Porter, V. R., Buxton, W. G., Fairbanks, L. A., Strickland, T., O'Connor, S. M., Rosenberg-Thompson, S. et al. (2003). Frequency and characteristics of anxiety among patients with Alzheimer's disease and related dementias. *The Journal of Neuropsychiatry and Clinical Neurosciences, 15*(2), 180-186.

Potter, G. G., Plassman, B. L., Burke, J. R., Kabeto, M. U., Langa, K. M., Llewellyn, D. J. et al. (2009). Cognitive performance and informant reports in the diagnosis of cognitive impairment and dementia in African Americans and whites. *Alzheimers & Dementia, 5*(6), 445-453. doi:10.1016/j.jalz.2009.04.1234

Price, J. L., McKeel, D. W., Jr., Buckles, V. D., Roe, C. M., Xiong, C., Grundman, M. et al. (2009). Neuropathology of nondemented aging: presumptive evidence for preclinical Alzheimer disease. *Neurobiology of Aging, 30*(7), 1026-1036. doi:10.1016/j.neurobiolaging.2009.04.002

Prince, M. (2000). Dementia in developing countries. A consensus statement from the 10/66 Dementia Research Group. *International Journal of Geriatric Psychiatry 15*(1), 14-20. doi:10.1002/(SICI)1099-1166(200001)15:1<14

Prince, M. (2004). Care arrangements for people with dementia in developing countries. *International Journal of Geriatric Psychiatry*, *19*(2), 170-177. doi:10.1002/gps.1046

Prince, M., Acosta, D., Chiu, H., Scazufca, M., & Varghese, M. (2003). Dementia diagnosis in developing countries: a cross-cultural validation study. *Lancet*, *361*(9361), 909-917. doi:10.1016/S0140-6736(03)12772-9

Qiu, C. (2012). Preventing Alzheimer's disease by targeting vascular risk factors: hope and gap. *Journal of Alzheimers Disease*, *32*(3), 721-731. doi:10.3233/JAD-2012-120922

Qiu, C., Backman, L., Winblad, B., Aguero-Torres, H., & Fratiglioni, L. (2001). The influence of education on clinically diagnosed dementia incidence and mortality data from the Kungsholmen Project. *Archives of Neurology*, *58*(12), 2034-2039.

Qureshi, S. U., Kimbrell, T., Pyne, J. M., Magruder, K. M., Hudson, T. J., Petersen, N. J. et al. (2010). Greater prevalence and incidence of dementia in older veterans with posttraumatic stress disorder. *Journal of the American Geriatrics Society*, *58*(9), 1627-1633. doi:10.1111/j.1532-5415.2010.02977.x

Rabbitt, P., Donlan, C., Watson, P., McInnes, L., & Bent, N. (1995). Unique and interactive effects of depression, age, socioeconomic advantage, and gender on cognitive performance of normal healthy older people. *Psychology and Aging*, *10*(3), 307-313.

Rainer, M., Wuschitz, A., Jagsch, C., Erb, C., Chirikdjian, J. J., & Mucke, H. A. (2011). Memantine in moderate to severe Alzheimer's disease: an observational post-marketing study. *Journal of Neural Transmission*, *118*(8), 1255-1259. doi:10.1007/s00702-011-0623-8

Rait, G., Walters, K., Bottomley, C., Petersen, I., Iliffe, S., & Nazareth, I. (2010). Survival of people with clinical diagnosis of dementia in primary care: cohort study. *British Medical Journal*, *341*, c3584.

Ramani, A., Jensen, J. H., & Helpern, J. A. (2006). Quantitative MR imaging in Alzheimer disease. *Radiology*, *241*(1), 26-44. doi:10.1148/radiol.2411050628

Raygani, A. V., Zahrai, M., Raygani, A. V., Doosti, M., Javadi, E., Rezaei, M. et al. (2005). Association between apolipoprotein E polymorphism and Alzheimer disease in Tehran, Iran. *Neuroscience Letters*, *375*(1), 1-6. doi:10.1016/j.neulet.2004.10.073

Reilly, D. (2012). Gender, culture, and sex-typed cognitive abilities. *PloS one*, *7*(7), e39904. doi:10.1371/journal.pone.0039904

Reitan R. M. & Wolfson, D. (1985). *The Halstead-Reitan Neuropsychological Test Battery: Therapy and clinical interpretation*. Tucson, AZ: Neuropsychological Press.

Reitz, C., Brayne, C., & Mayeux, R. (2011). Epidemiology of Alzheimer disease. *Nature Review Neurology*, *7*(3), 137-152. doi:10.1038/nrneurol.2011.2

Rembach, A., Faux, N. G., Watt, A. D., Pertile, K. K., Rumble, R. L., Trounson, B. O. et al. (2013). Changes in plasma amyloid beta in a longitudinal study of aging and Alzheimer's disease. *Alzheimer's & Dementia*, doi:10.1016/j.jalz.2012.12.006

Reser, J. E. (2009). Alzheimer's disease and natural cognitive aging may represent adaptive metabolism reduction programs. *Behavioral and Brain Functions*, *5*13. doi:10.1186/1744-9081-5-13

Richards, M. & Sacker, A. (2003). Lifetime antecedents of cognitive reserve. *Journal of Clinical and Experimental Neuropsychology, 25*(5), 614-624. doi:10.1076/jcen.25.5.614.14581

Richardson, T. J., Lee, S. J., Berg-Weger, M., & Grossberg, G. T. (2013). Caregiver health: health of caregivers of Alzheimer's and other dementia patients. *Current Psychiatry Reports*, *15*(7), 367. doi:10.1007/s11920-013-0367-2

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

Rimmele, U., Seiler, R., Marti, B., Wirtz, P. H., Ehlert, U., & Heinrichs, M. (2009). The level of physical activity affects adrenal and cardiovascular reactivity to psychosocial stress. *Psychoneuroendocrinology, 34*(2), 190-198. doi: 10.1016/j.psyneuen.2008.08.023

Rissman, R. A., Trojanowski, J. Q., Shaw, L. M., & Aisen, P. S. (2012). Longitudinal plasma amyloid beta as a biomarker of Alzheimer's disease. *Journal of Neural Transmission, 119*(7), 843-850. doi:10.1007/s00702-012-0772-4

Ritchie, K. & Führer, R. (1996). The validation of an informant screening test for irreversible cognitive decline in the elderly: within a general population sample. *International Journal of Geriatric Psychiatry, 11*(2), 149-156. doi: 10.1002/(SICI)1099-1166(199602)11:2<149

Roberts, A. D., Wessely, S., Chalder, T., Papadopoulos, A., & Cleare, A. J. (2004). Salivary cortisol response to awakening in chronic fatigue syndrome. *British Journal of Psychiatry*, *184*, 136-141.

Rodriguez, H., Brathwaite, D., & Dorsey, S. (2002). Depression and social support in the elderly population: a study of rural South African elders. *Association of Black Nursing Faculty in Higher Education Journal, 13*(2), 45-48.

Roe, C. M., Xiong, C., Miller, J. P., & Morris, J. C. (2007). Education and Alzheimer disease without dementia: support for the cognitive reserve hypothesis. *Neurology, 68*(3), 223-228. doi:10.1212/01.wnl.0000251303.50459.8a

Roher, A. E., Lowenson, J. D., Clarke, S., Woods, A. S., Cotter, R. J., Gowing, E. et al. (1993). beta-Amyloid-(1-42) is a major component of cerebrovascular amyloid deposits: implications for the pathology of Alzheimer disease. *Proceedings of*

the National Academy of Sciences of the United States of America, *90*(22), 10836-10840.

Romero, L. M. & Butler, L. K. (2007). Endocrinology of Stress. *International Journal of Comparative Psychology*, *20*89-95.

Roozendaal, B. (2000). 1999 Curt P. Richter award. Glucocorticoids and the regulation of memory consolidation. *Psychoneuroendocrinology*, *25*(3), 213-238. doi:S030645309900058X [pii]

Ropper A. H. & Brown, R. J. (2005). *Principles of Neurology.* New York: McGraw-Hill.

Rosselli, M. & Ardila, A. (2003). The impact of culture and education on non-verbal neuropsychological measurements: a critical review. *Brain and Cognition, 52*(3), 326-333.

Royall, D. R., Cordes, J. A., & Polk, M. (1998). CLOX: an executive clock drawing task. *Journal of Neurology, Neurosurgery, and Psychiatry*, *64*(5), 588-594.

Russo, S. J., Murrough, J. W., Han, M. H., Charney, D. S., & Nestler, E. J. (2012). Neurobiology of resilience. *Nature Neuroscience*, *15*(11), 1475-1484. doi:10.1038/nn.3234

Sahota, A., Yang, M., Gao, S., Hui, S. L., Baiyewu, O., Gureje, O. et al. (1997). Apolipoprotein E-associated risk for Alzheimer's disease in the African-American population is genotype dependent. *Annals of Neurology*, *42*(4), 659-661. doi:10.1002/ana.410420418 [doi]

Salmon, D. P. & Bondi, M. W. (2009). Neuropsychological assessment of dementia. *Annual Review of Psychology*, 60, 257-282. doi:10.1146/annurev.psych.57.102904.190024

Salthouse, T. A. (2009). When does age-related cognitive decline begin? *Neurobiological Aging*, *30*(4), 507-514. doi:10.1016/j.neurobiolaging.2008.09.023

Samplin, E., Ikuta, T., Malhotra, A. K., Szeszko, P. R., & Derosse, P. (2013). Sex differences in resilience to childhood maltreatment: Effects of trauma history on hippocampal volume, general cognition and subclinical psychosis in healthy adults. *Journal of Psychiatric Research*, *47*(9), 1174-1179. doi:10.1016/j.jpsychires.2013.05.008

Samuelson, K. W. (2011). Post-traumatic stress disorder and declarative memory functioning: a review. *Dialogues in Clinical NeuroSciences*, *13*(3), 346-351.

Sanchez, M. M., Young, L. J., Plotsky, P. M., & Insel, T. R. (2000). Distribution of corticosteroid receptors in the rhesus brain: relative absence of glucocorticoid receptors in the hippocampal formation. *Journal of Neuroscience*, *20*(12), 4657-4668. doi:20/12/4657

Sandholzer, C., Delport, R., Vermaak, H., & Utermann, G. (1995). High frequency of the apo epsilon 4 allele in Khoi San from South Africa. *Human Genetics, 95*(1), 46-48.

Sandi, C. (2013). Stress and Cognition. *Wiley Interdisciplinary Reviews: Cognitive Science, 4*(3), 245-261. doi:10.1002/wcs.1222

Sando, S. B., Melquist, S., Cannon, A., Hutton, M., Sletvold, O., Saltvedt, I. et al. (2008a). Risk-reducing effect of education in Alzheimer's disease. *International Journal of Geriatric Psychiatry, 23*(11), 1156-1162. doi:10.1002/gps.2043

Sando, S. B., Melquist, S., Cannon, A., Hutton, M. L., Sletvold, O., Saltvedt, I. et al. (2008b). APOE epsilon 4 lowers age at onset and is a high risk factor for Alzheimer's disease; a case control study from central Norway. *BMC Neurology, 8*9. doi:10.1186/1471-2377-8-9

Sandstrom, A., Peterson, J., Sandstrom, E., Lundberg, M., Nystrom, I. L., Nyberg, L. et al. (2011). Cognitive deficits in relation to personality type and hypothalamic-pituitary-adrenal (HPA) axis dysfunction in women with stress-related exhaustion. *Scandinavian Journal of Psychology, 52*(1), 71-82. doi:10.1111/j.1467-9450.2010.00844.x

Sapolsky, R. M. (1996). Why stress is bad for your brain. *Science, 273*(5276), 749-750.

Sapolsky, R. M. (1999). Glucocorticoids, stress, and their adverse neurological effects: relevance to aging. *Experimental Gerontology, 34*(6), 721-732.

Sapolsky, R. M. (2000). Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. *Archives of General Psychiatry, 57*(10), 925-935.

Sapolsky, R. M. (2002). Chickens, eggs and hippocampal atrophy. *Nature Neuroscience, 5*(11), 1111-1113. doi:10.1038/nn1102-1111

Sapolsky, R. M., Krey, L. C., & McEwen, B. S. (1986). The neuroendocrinology of stress and aging: the glucocorticoid cascade hypothesis. *Endocrine Reviews, 7*(3), 284-301.

Sarsour, K., Sheridan, M., Jutte, D., Nuru-Jeter, A., Hinshaw, S., & Boyce, W. T. (2011). Family socioeconomic status and child executive functions: the roles of language, home environment, and single parenthood. *Journal of the International Neuropsychological Society, 17*(1), 120-132. doi:10.1017/S1355617710001335

Sattler, C., Erickson, K. I., Toro, P., & Schroder, J. (2011). Physical fitness as a protective factor for cognitive impairment in a prospective population-based study in Germany. *Journal of Alzheimers Disease, 26*(4), 709-718. doi:10.3233/JAD-2011-110548

Sayi, J. G., Patel, N. B., Premkumar, D. R., Adem, A., Winblad, B., Matuja, W. B. et al. (1997). Apolipoprotein E polymorphism in elderly east Africans. *East African Medical Journal, 74*(10), 668-670.

Scahill, R. I., Schott, J. M., Stevens, J. M., Rossor, M. N., & Fox, N. C. (2002). Mapping the evolution of regional atrophy in Alzheimer's disease: unbiased analysis of fluid-registered serial MRI. *Proceedings of the National Academy of Sciences of the United States of America*, *99*(7), 4703-4707. doi:10.1073/pnas.052587399

Scarmeas, N., Albert, S. M., Manly, J. J., & Stern, Y. (2006). Education and rates of cognitive decline in incident Alzheimer's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, *77*(3), 308-316. doi:10.1136/jnnp.2005.072306

Scazufca, M., Menezes, P. R., Araya, R., Di Rienzo, V. D., Almeida, O. P., Gunnell, D. 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), 879-890. doi:10.1093/ije/dyn125

Schiepers, O. J., Harris, S. E., Gow, A. J., Pattie, A., Brett, C. E., Starr, J. M. et al. (2012). APOE E4 status predicts age-related cognitive decline in the ninth decade: longitudinal follow-up of the Lothian Birth Cohort 1921. *Molecular Psychiatry*, *17*(3), 315-324. doi:10.1038/mp.2010.137

Schmidt, R., Kienbacher, E., Benke, T., Dal-Bianco, P., Delazer, M., Ladurner, G. et al. (2008). Sex differences in Alzheimer's disease. *Neuropsychiatry*, *22*(1), 1-15.

Schmitt, F. A. & Wichems, C. H. (2006). A systematic review of assessment and treatment of moderate to severe Alzheimer's disease. *Primary Care Companion - Journal of Clinical Psychiatry*, *8*(3), 158-159.

Schneider, A. L., Sharrett, A. R., Patel, M. D., Alonso, A., Coresh, J., Mosley, T. et al. (2012). Education and cognitive change over 15 years: the atherosclerosis risk in communities study. *Journal of the American Geriatrics Society*, *60*(10), 1847-1853. doi:10.1111/j.1532-5415.2012.04164.x

Schoon I. (2006). *Risk and Resilience: Adaptations in Changing Times.* Cambridge: Cambridge University Press.

Schrijvers, E. M., Direk, N., Koudstaal, P. J., Kirschbaum, C., Hofman, A., Tiemeier, H. et al. (2011). Associations of serum cortisol with cognitive function and dementia: the Rotterdam Study. *Journal of Alzheimer's Disease*, *25*(4), 671-677. doi:10.3233/JAD-2011-110224

Schuff, N., Woerner, N., Boreta, L., Kornfield, T., Shaw, L. M., Trojanowski, J. Q. et al. (2009). MRI of hippocampal volume loss in early Alzheimer's disease in relation to ApoE genotype and biomarkers. *Brain*, *132*(Pt 4), 1067-1077. doi:10.1093/brain/awp007

Schupf, N., Tang, M. X., Fukuyama, H., Manly, J., Andrews, H., Mehta, P. et al. (2008). Peripheral Abeta subspecies as risk biomarkers of Alzheimer's disease. *Proceedings of the National Academy of Sciences of the United States of America*, *105*(37), 14052-14057. doi:10.1073/pnas.0805902105

Scully, D., Kremer, J., Meade, M. M., Graham, R., & Dudgeon, K. (1998). Physical exercise and psychological well being: a critical review. *British Journal of Sports Medicine, 32*(2), 111-120.

Segonne, F., Pacheco, J., & Fischl, B. (2007). Geometrically accurate topology-correction of cortical surfaces using nonseparating loops. *IEEE Transactions on Medical Imaging, 26*(4), 518-529. doi:10.1109/TMI.2006.887364

Selkoe, D. J. (2003). Folding proteins in fatal ways. *Nature, 426*(6968), 900-904. doi:10.1038/nature02264

Selye H. (1976). *The stress of life.* New York: The McGraw-Hill Companies, Inc.

Sepehrnia, B., Kamboh, M. I., Adams-Campbell, L. L., Bunker, C. H., Nwankwo, M., Majumder, P. P. et al. (1989). Genetic studies of human apolipoproteins. X. The effect of the apolipoprotein E polymorphism on quantitative levels of lipoproteins in Nigerian blacks. *American Journal of Human Genetics, 45*(4), 586-591.

Serrano-Pozo, A., Frosch, M. P., Masliah, E., & Hyman, B. T. (2011). Neuropathological alterations in Alzheimer disease. *Cold Spring Harbor Perspectives in Medicine, 1*(1), a006189. doi:10.1101/cshperspect.a006189

Shaji, S., Bose, S., & Verghese, A. (2005). Prevalence of dementia in an urban population in Kerala, India. *The British Journal of Psychiatry, 186,* 136-140. doi:10.1192/bjp.186.2.136

Sharp, E. S. & Gatz, M. (2011). Relationship between education and dementia: an updated systematic review. *Alzheimer Disease and Associated Disorders, 25*(4), 289-304. doi:10.1097/WAD.0b013e318211c83c

Sheng, M., Sabatini, B. L., & Sudhof, T. C. (2012). Synapses and Alzheimer's disease. *Cold Spring Harbor Perspectives in Biology, 2012/04/12*doi:10.1101/cshperspect.a005777

Shirtcliff, E. A., Allison, A. L., Armstrong, J. M., Slattery, M. J., Kalin, N. H., & Essex, M. J. (2012). Longitudinal stability and developmental properties of salivary cortisol levels and circadian rhythms from childhood to adolescence. *Developmental Psychobiology, 54*(5), 493-502. doi:10.1002/dev.20607

Shon, J. M., Lee, D. Y., Seo, E. H., Sohn, B. K., Kim, J. W., Park, S. Y. et al. (2013). Functional neuroanatomical correlates of the executive clock drawing task (CLOX) performance in Alzheimer's disease: A FDG-PET study. *Neuroscience, (246)* 271-280. doi:.1016/j.neuroscience.2013.05.008

Shuttleworth-Edwards, A. B., Kemp, R. D., Rust, A. L., Muirhead, J. G., Hartman, N. P., & Radloff, S. E. (2004). Cross-cultural effects on IQ test performance: a review and preliminary normative indications on WAIS-III test performance. *Journal of Clinical and Experimental Neuropsychology, 26*(7), 903-920. doi:10.1080/13803390490510824

Shuttleworth-Jordan, A. B. (1996). On not reinventing the wheel. A clinical perspective on culturally relevant test usage in South Africa. *South African Journal of Psychology, 26*(2), 96-102.

Siegrist, J., Lunau, T., Wahrendorf, M., & Dragano, N. (2012). Depressive symptoms and psychosocial stress at work among older employees in three continents. *Global Health, (8)*27. doi:10.1186/1744-8603-8-27

Singh, P. P., Singh, M., & Mastana, S. S. (2006). APOE distribution in world populations with new data from India and the UK. *Annals of Human Biology, 33*(3), 279-308. doi:10.1080/03014460600594513

Sivanandam, T. M. & Thakur, M. K. (2012). Traumatic brain injury: a risk factor for Alzheimer's disease. *Neuroscience and Biobehavioral Reviews, 36*(5), 1376-1381. doi:10.1016/j.neubiorev.2012.02.013

Slavin, M. J., Sandstrom, C. K., Tran, T. T., Doraiswamy, P. M., & Petrella, J. R. (2007). Hippocampal volume and the Mini-Mental State Examination in the diagnosis of amnestic mild cognitive impairment. *American Journal of Roentgenology, 188*(5), 1404-1410. doi:10.2214/AJR.06.1052

Sliwinski, M., Lipton, R. B., Buschke, H., & Stewart, W. (1996). The effects of preclinical dementia on estimates of normal cognitive functioning in aging. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences, 51*(4), 217-225.

Sled, J. G., Zijdenbos, A. P., & Evans, A. C. (1998). A nonparametric method for automatic correction of intensity nonuniformity in MRI data. *IEEE Transactions on Medical Imaging, 17*(1), 87-97. doi:10.1109/42.668698

Small, B. J., Mobly, J. L., Laukka, E. J., Jones, S., & Backman, L. (2003). Cognitive deficits in preclinical Alzheimer's disease. *Acta Neurologica Scandinavica, Suppl 17*, 929-33.

Small, B. J., Rosnick, C. B., Fratiglioni, L., & Backman, L. (2004). Apolipoprotein E and cognitive performance: a meta-analysis. *Psychology and Aging, 19*(4), 592-600. doi:10.1037/0882-7974.19.4.592

Smith, M. E. (2005). Bilateral hippocampal volume reduction in adults with post-traumatic stress disorder: a meta-analysis of structural MRI studies. *Hippocampus, 15*(6), 798-807. doi:10.1002/hipo.20102

Solas, M., Aisa, B., Mugueta, M. C., Del, R. J., Tordera, R. M., & Ramirez, M. J. (2010). Interactions between age, stress and insulin on cognition: implications for Alzheimer's disease. *Neuropsychopharmacology, 35*(8), 1664-1673. doi:10.1038/npp.2010.13

Sondag, C. M., Dhawan, G., & Combs, C. K. (2009). Beta amyloid oligomers and fibrils stimulate differential activation of primary microglia. *Journal of Neuroinflammation, 6*1. doi:10.1186/1742-2094-6-1

Song, F., Poljak, A., Valenzuela, M., Mayeux, R., Smythe, G. A., & Sachdev, P. S. (2011). Meta-analysis of plasma amyloid-beta levels in Alzheimer's disease. *Journal of Alzheimer's Disease, 26*(2), 365-375. doi:10.3233/JAD-2011-101977

Soonawala, D., Amin, T., Ebmeier, K. P., Steele, J. D., Dougall, N. J., Best, J. et al. (2002). Statistical parametric mapping of (99m)Tc-HMPAO-SPECT images for the diagnosis of Alzheimer's disease: normalizing to cerebellar tracer uptake. *Neuroimage, 17*(3), 1193-1202.

Sotiropoulos, I., Cerqueira, J. J., Catania, C., Takashima, A., Sousa, N., & Almeida, O. F. (2008). Stress and glucocorticoid footprints in the brain-the path from depression to Alzheimer's disease. *Neuroscience and Biobehavioral Reviews, 32*(6), 1161-1173. doi:10.1016/j.neubiorev.2008.05.007

Spampinato, M. V., Rumboldt, Z., Hosker, R. J., & Mintzer, J. E. (2011). Apolipoprotein E and gray matter volume loss in patients with mild cognitive impairment and Alzheimer disease. *Radiology, 258*(3), 843-852. doi:10.1148/radiol.10100307

Sperling, R. A., Aisen, P. S., Beckett, L. A., Bennett, D. A., Craft, S., Fagan, A. M. et al. (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. *Alzheimers & Dementia, 7*(3), 280-292. doi:10.1016/j.jalz.2011.03.003

Squire, L. R. (1992). Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. *Psychological Review, 99*(2), 195-231.

Srivareerat, M., Tran, T. T., Alzoubi, K. H., & Alkadhi, K. A. (2009). Chronic psychosocial stress exacerbates impairment of cognition and long-term potentiation in beta-amyloid rat model of Alzheimer's disease. *Biological Psychiatry, 65*(11), 918-926. doi:10.1016/j.biopsych.2008.08.021

Statistics South Africa. (2013). Mid-year population estimates. *P0302*1-17.

Stawski, R. S., Sliwinski, M. J., Almeida, D. M., & Smyth, J. M. (2008). Reported exposure and emotional reactivity to daily stressors: the roles of adult age and global perceived stress. *Psychology & Aging, 23*(1), 52-61. doi:2008-02853-007

Stawski, R. S., Sliwinski, M. J., & Smyth, J. M. (2006). Stress-related cognitive interference predicts cognitive function in old age. *Psychology and Aging, 21*(3), 535-544. doi:10.1037/0882-7974.21.3.535

Steffens, D. C., McQuoid, D. R., Payne, M. E., & Potter, G. G. (2011). Change in hippocampal volume on magnetic resonance imaging and cognitive decline among older depressed and nondepressed subjects in the neurocognitive outcomes of depression in the elderly study. *The American Journal of Geriatric Psychiatry, 19*(1), 4-12. doi:10.1097/JGP.0b013e3181d6c245

Steffens, D. C., Otey, E., Alexopoulos, G. S., Butters, M. A., Cuthbert, B., Ganguli, M. et al. (2006). Perspectives on depression, mild cognitive impairment, and

cognitive decline. *Archives of General Psychiatry*, *63*(2), 130-138. doi:63/2/130 [pii];10.1001/archpsyc.63.2.130

Stein, D. J., Ipser, J. C., & Seedat, S. (2006). Pharmacotherapy for post traumatic stress disorder (PTSD). *Cochrane Database Systematic Reviews*, (1), CD002795. doi:10.1002/14651858.CD002795.pub2

Sterlemann, V., Rammes, G., Wolf, M., Liebl, C., Ganea, K., Muller, M. B. et al. (2010). Chronic social stress during adolescence induces cognitive impairment in aged mice. *Hippocampus*, *20*(4), 540-549. doi:10.1002/hipo.20655

Sterling, P. & Eyer, J. (1988). Allostasis: a new paradigm to explain arousal pathology. In *Handbook of life stress, cognition and health* (pp. 629-649) New York: John Wiley & Sons.

Stern, R. G., Mohs, R. C., Davidson, M., Schmeidler, J., Silverman, J., Kramer-Ginsberg, E. et al. (1994a). A longitudinal study of Alzheimer's disease: measurement, rate, and predictors of cognitive deterioration. *American Journal of Psychiatry*, *151*(3), 390-396.

Stern, Y. (2009). Cognitive reserve. *Neuropsychologia*, *47*(10), 2015-2028. doi:10.1016/j.neuropsychologia.2009.03.004

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*(13), 1004-1010.

Stern, Y., Tang, M. X., Denaro, J., & Mayeux, R. (1995). Increased risk of mortality in Alzheimer's disease patients with more advanced educational and occupational attainment. *Annals of Neurology*, *37*(5), 590-595. doi:10.1002/ana.410370508

Steyn, L. (2010). Dementia: SA's hidden disease. *Mail & Guardian*. Retrieved from http://mg.co.za/article/2010-10-08-dementia-sas-hidden-disease

Strassnig, M. & Ganguli, M. (2005). About a peculiar disease of the cerebral cortex: Alzheimer's original case revisited. *Psychiatry (Edgmont.)*, *2*(9), 30-33.

Strauss E., Sherman, E. M. S., & Spreen, O. (2006). *A Compendium of neuropsychological tests: Administration, norms, and commentary.* New York: Oxford University Press.

Stricks, L., Pittman, J., Jacobs, D. M., Sano, M., & Stern, Y. (1998). Normative data for a brief neuropsychological battery administered to English- and Spanish-speaking community-dwelling elders. *Journal of the International Neuropsychological Society*, *4*(4), 311-318.

Stromberg, R., Backlund, L. G., & Lofvander, M. (2011). Psychosocial stressors and depression at a Swedish primary health care centre. A gender perspective study. *BMC Family Practice*, *(12)*120. doi:1471-2296-12-120

Stutts, J. C., Stewart, J. R., & Martell, C. (1998). Cognitive test performance and crash risk in an older driver population. *Accident Analysis & Prevention*, *30*(3), 337-346.

Suh, G. H., Ju, Y. S., Yeon, B. K., & Shah, A. (2004). A longitudinal study of Alzheimer's disease: rates of cognitive and functional decline. *International Journal of Geriatric Psychiatry*, *19*(9), 817-824. doi:10.1002/gps.1168

Sundelof, J., Giedraitis, V., Irizarry, M. C., Sundstrom, J., Ingelsson, E., Ronnemaa, E. et al. (2008). Plasma beta amyloid and the risk of Alzheimer disease and dementia in elderly men: a prospective, population-based cohort study. *Archives of Neurology*, *65*(2), 256-263. doi:10.1001/archneurol.2007.57

Swanwick, G. R., Kirby, M., Bruce, I., Buggy, F., Coen, R. F., Coakley, D. et al. (1998b). Hypothalamic-pituitary-adrenal axis dysfunction in Alzheimer's disease: lack of association between longitudinal and cross-sectional findings. *American Journal of Psychiatry*, *155*(2), 286-289.

Szeszko, P. R., Betensky, J. D., Mentschel, C., Gunduz-Bruce, H., Lencz, T., Ashtari, M. et al. (2006). Increased stress and smaller anterior hippocampal volume. *NeuroReport*, *17*(17), 1825-1828. doi:10.1097/01.wnr.0000246322.58814.b8

Szwast, S. J., Hendrie, H. C., Lane, K. A., Gao, S., Taylor, S. E., Unverzagt, F. et al. (2007). Association of statin use with cognitive decline in elderly African Americans. *Neurology*, *69*(19), 1873-1880. doi:10.1212/01.wnl.0000279333.77404.d7

Takahashi, R. H., Nam, E. E., Edgar, M., & Gouras, G. K. (2002). Alzheimer beta-amyloid peptides: normal and abnormal localization. *Histology and Histopathology*, *17*(1), 239-246.

Tasker, J. G. & Herman, J. P. (2011). Mechanisms of rapid glucocorticoid feedback inhibition of the hypothalamic-pituitary-adrenal axis. *Stress*, *14*(4), 398-406. doi:10.3109/10253890.2011.586446

Taylor, M., Barr, M., Stevens, G., Bryson-Taylor, D., Agho, K., Jacobs, J. et al. (2010). Psychosocial stress and strategies for managing adversity: measuring population resilience in New South Wales, Australia. *Population Health Metrics*, *8,* 28. doi:10.1186/1478-7954-8-28

Teri, L., Ferretti, L. E., Gibbons, L. E., Logsdon, R. G., McCurry, S. M., Kukull, W. A. et al. (1999). Anxiety of Alzheimer's disease: prevalence, and comorbidity. *The Journals of Gerontology: Series A: Biological Sciences and Medical Sciences*, *54*(7), 348-352.

Teri, L., McCurry, S. M., Edland, S. D., Kukull, W. A., & Larson, E. B. (1995). Cognitive decline in Alzheimer's disease: a longitudinal investigation of risk factors for accelerated decline. *The Journals of Gerontology: Series A: Biological Sciences and Medical Sciences*, *50A*(1), 49-55.

Terracciano, A., Iacono, D., O'Brien, R. J., Troncoso, J. C., An, Y., Sutin, A. R. et al. (2013). Personality and resilience to Alzheimer's disease neuropathology: a

prospective autopsy study. *Neurobiology of Aging*, *34*(4), 1045-1050. doi:10.1016/j.neurobiolaging.2012.08.008

Tessner, K. D., Walker, E. F., Dhruv, S. H., Hochman, K., & Hamann, S. (2007). The relation of cortisol levels with hippocampus volumes under baseline and challenge conditions. *Brain Research*, *1179*70-78. doi:10.1016/j.brainres.2007.05.027

Toepper, M., Beblo, T., Thomas, C., & Driessen, M. (2008). Early detection of Alzheimer's disease: a new working memory paradigm. *International Journal of Geriatric Psychiatry*, *23*(3), 272-278. doi:10.1002/gps.1873

Toledo, J. B., Shaw, L. M., & Trojanowski, J. Q. (2013). Plasma amyloid beta measurements - a desired but elusive Alzheimer's disease biomarker. *Alzheimers Research & Therapy*, *5*(2), 8. doi:10.1186/alzrt162

Toledo, J. B., Toledo, E., Weiner, M. W., Jack, C. R., Jr., Jagust, W., Lee, V. M. et al. (2012). Cardiovascular risk factors, cortisol, and amyloid-beta deposition in Alzheimer's Disease Neuroimaging Initiative. *Alzheimers & Dementia*, *8*(6), 483-489. doi:10.1016/j.jalz.2011.08.008

Torres, A., Gomez-Gil, E., Vidal, A., Puig, O., Boget, T., & Salamero, M. (2006). Gender differences in cognitive functions and influence of sex hormones. *Actas Españolas de Psiquiatría*, *34*(6), 408-415.

Tsai, M. S., Tangalos, E. G., Petersen, R. C., Smith, G. E., Schaid, D. J., Kokmen, E. et al. (1994). Apolipoprotein E: risk factor for Alzheimer disease. *American Journal of Human Genetics*, *54*(4), 643-649.

Tsang, P. S. & Shaner, T. L. (1998). Age, attention, expertise, and time-sharing performance. *Psychology and Aging*, *13*(2), 323-347.

Tschanz, J. T., Pfister, R., Wanzek, J., Corcoran, C., Smith, K., Tschanz, B. T. et al. (2012). Stressful life events and cognitive decline in late life: moderation by education and age. The Cache County Study. *International Journal of Geriatric Psychiatry*. doi:10.1002/gps.3888

Tschanz, J. T., Welsh-Bohmer, K. A., Lyketsos, C. G., Corcoran, C., Green, R. C., Hayden, K. et al. (2006). Conversion to dementia from mild cognitive disorder: the Cache County Study. *Neurology*, *67*(2), 229-234. doi:10.1212/01.wnl.0000224748.48011.84

Tsigos, C. & Chrousos, G. P. (2002). Hypothalamic-pituitary-adrenal axis, neuroendocrine factors and stress. *Journal of Psychosomatic Research*, *53*(4), 865-871.

Tsolaki, M., Eleftheriou, M., & Karavida, N. (2009). Alzheimer's dementia and post-traumatic stress disorder differences and similarities in neuroimaging. *Hellenic Society of Nuclear Medicine*, *12*(1), 41-46.

Tucker, A. M. & Stern, Y. (2011). Cognitive reserve in aging. *Current Alzheimer Research*, *8*(4), 354-360.

Umegaki, H., Iimuro, S., Shinozaki, T., Araki, A., Sakurai, T., Iijima, K. et al. (2012). Risk factors associated with cognitive decline in the elderly with type 2 diabetes: baseline data analysis of the Japanese Elderly Diabetes Intervention Trial. *Geriatrics & Gerontology International*, *12 Suppl 1*103-109. doi:10.1111/j.1447-0594.2011.00817.x

Umegaki, H., Ikari, H., Nakahata, H., Endo, H., Suzuki, Y., Ogawa, O. et al. (2000). Plasma cortisol levels in elderly female subjects with Alzheimer's disease: a cross-sectional and longitudinal study. *Brain Research, 881*(2), 241-243.

Umeora, O. U. & Egwuatu, V. E. (2009). Obstetric performance recall accuracy (OPERA) among a low literacy population in Southeast Nigeria. *Nigerian Journal of Clinical Practice, 12*(4), 362-366.

United Nations Population Division. (2006). *World Population Prospects, 2004.* New York: United Nations Population Division.

University of the Free State. (2010). Higher than expected prevalence of dementia in South African urban black population. Retrieved from http://www.ufs.ac.za/templates/archive.aspx?news=1871&cat=1.

Unverzagt, F. W., Hui, S. L., Farlow, M. R., Hall, K. S., & Hendrie, H. C. (1998). Cognitive decline and education in mild dementia. *Neurology, 50*(1), 181-185.

Unverzagt, F. W., Ogunniyi, A., Taler, V., Gao, S., Lane, K. A., Baiyewu, O. et al. (2011). Incidence and risk factors for cognitive impairment no dementia and mild cognitive impairment in African Americans. *Alzheimer Disease and Associated Disorders*, *25*(1), 4-10. doi:10.1097/WAD.0b013e3181f1c8b1

Vagelatos, N. T. & Eslick, G. D. (2013). Type 2 Diabetes as a Risk Factor for Alzheimer's Disease: The Confounders, Interactions, and Neuropathology Associated With This Relationship. *Epidemiologic Reviews*, doi:10.1093/epirev/mxs012

Vaiva, G., Ducrocq, F., Jezequel, K., Averland, B., Lestavel, P., Brunet, A. et al. (2003). Immediate treatment with propranolol decreases posttraumatic stress disorder two months after trauma. *Biological Psychiatry*, *54*(9), 947-949.

van Hooren, S. A., Valentijn, A. M., Bosma, H., Ponds, R. W., van Boxtel, M. P., & Jolles, J. (2007). Cognitive functioning in healthy older adults aged 64-81: a cohort study into the effects of age, sex, and education. *Neuropsychology, Development, and Cognition. Section B, Aging, Neuropsychology and Cognition*, *14*(1), 40-54. doi:10.1080/138255890969483

van Oijen, M., Hofman, A., Soares, H. D., Koudstaal, P. J., & Breteler, M. M. (2006). Plasma Abeta(1-40) and Abeta(1-42) and the risk of dementia: a prospective case-cohort study. *Lancet Neurology, 5*(8), 655-660. doi:10.1016/S1474-4422(06)70501-4

van Santen, A., Vreeburg, S. A., Van der Does, A. J., Spinhoven, P., Zitman, F. G., & Penninx, B. W. (2011). Psychological traits and the cortisol awakening response: results from the Netherlands Study of Depression and Anxiety.

Psychoneuroendocrinology, *36*(2), 240-248. doi:10.1016/j.psyneuen.2010.07.014

Vasterling, J. J., Brailey, K., Proctor, S. P., Kane, R., Heeren, T., & Franz, M. (2012). Neuropsychological outcomes of mild traumatic brain injury, post-traumatic stress disorder and depression in Iraq-deployed US Army soldiers. *British Journal of Psychiatry, 201*(3), 186-192. doi:10.1192/bjp.bp.111.096461

Vemuri, P., Wiste, H. J., Weigand, S. D., Shaw, L. M., Trojanowski, J. Q., Weiner, M. W. et al. (2009). MRI and CSF biomarkers in normal, MCI, and AD subjects: predicting future clinical change. *Neurology, 73*(4), 294-301. doi:73/4/294

Verbeek, M. M., Eikelenboom, P., & de Waal, R. M. (1997). Differences between the pathogenesis of senile plaques and congophilic angiopathy in Alzheimer disease. *Journal of Neuropathology & Experimental Neurology*, *56*(7), 751-761.

Verhaeghen, P. & Cerella, J. (2002). Aging, executive control, and attention: a review of meta-analyses. *Neuroscience and Biobehavioral Reviews, 26*(7), 849-857.

Vgontzas, A. N., Zoumakis, M., Bixler, E. O., Lin, H. M., Prolo, P., Vela-Bueno, A. et al. (2003). Impaired nighttime sleep in healthy old versus young adults is associated with elevated plasma interleukin-6 and cortisol levels: physiologic and therapeutic implications. *The Journal of Clinical Endocrinology and Metabolism*, *88*(5), 2087-2095.

Vijayakumar, A. & Vijayakumar, A. (2012). Comparison of hippocampal volume in dementia subtypes. *ISRN Radiology*, *2013*1-5.

Villarreal, G., Hamilton, D. A., Petropoulos, H., Driscoll, I., Rowland, L. M., Griego, J. A. et al. (2002). Reduced hippocampal volume and total white matter volume in posttraumatic stress disorder. *Biological Psychiatry*, *52*(2), 119-125.

Vina, J. & Lloret, A. (2010). Why women have more Alzheimer's disease than men: gender and mitochondrial toxicity of amyloid-beta peptide. *Journal of Alzheimer's disease, 20 Suppl 2*, S527-S533. doi:10.3233/JAD-2010-100501

Vitaliano, P. P., Echeverria, D., Yi, J., Phillips, P. E., Young, H., & Siegler, I. C. (2005). Psychophysiological mediators of caregiver stress and differential cognitive decline. *Psychology & Aging*, *20*(3), 402-411. doi:10.1037/0882-7974.20.3.402

Vlassoff, C. (2007). Gender differences in determinants and consequences of health and illness. *Journal of Health, Population and Nutrition*, *25*(1), 47-61.

Volpato, S., Guralnik, J. M., Fried, L. P., Remaley, A. T., Cappola, A. R., & Launer, L. J. (2002). Serum thyroxine level and cognitive decline in euthyroid older women. *Neurology*, *58*(7), 1055-1061.

Voyer, D., Voyer, S., & Bryden, M. P. (1995). Magnitude of sex differences in spatial abilities: a meta-analysis and consideration of critical variables. *Psychological Bulletin*, *117*(2), 250-270.

Wagnild, G. (2003). Resilience and successful aging. Comparison among low and high income older adults. *Journal of Gerontological Nursing*, *29*(12), 42-49.

Walsh, B., Slater, S., Nair, B., & Attia, J. (2013). The relationship between the apolipoprotein E e4 allele and hippocampal magnetic resonance imaging volume in community-dwelling individuals with mild Alzheimer's disease. *Degenerative Neurological ad Neuromuscular Disease*, *3*11-14. doi:10.2147/DNND.S40835

Wang, H. X., Wahlberg, M., Karp, A., Winblad, B., & Fratiglioni, L. (2012). Psychosocial stress at work is associated with increased dementia risk in late life. *Alzheimer's & Dementia*, *8*(2), 114-120. doi:10.1016/j.jalz.2011.03.001

Wang, J., Korczykowski, M., Rao, H., Fan, Y., Pluta, J., Gur, R. C. et al. (2007). Gender difference in neural response to psychological stress. *Social Cognitive and Affective Neuroscience*, *2*(3), 227-239. doi:10.1093/scan/nsm018

Watanabe, Y., Gould, E., & McEwen, B. S. (1992). Stress induces atrophy of apical dendrites of hippocampal CA3 pyramidal neurons. *Brain Research*, *588*(2), 341-345.

Wattmo, C., Wallin, A. K., Londos, E., & Minthon, L. (2011). Predictors of long-term cognitive outcome in Alzheimer's disease. *Alzheimer's Research & Therapy*, *3*(4), 23. doi:10.1186/alzrt85

Weaver, I. C., Diorio, J., Seckl, J. R., Szyf, M., & Meaney, M. J. (2004). Early environmental regulation of hippocampal glucocorticoid receptor gene expression: characterization of intracellular mediators and potential genomic target sites. *Annals of the New York Academy of Sciences*, *1024*, 182-212. doi:10.1196/annals.1321.099

Webster, M. J., Knable, M. B., O'Grady, J., Orthmann, J., & Weickert, C. S. (2002). Regional specificity of brain glucocorticoid receptor mRNA alterations in subjects with schizophrenia and mood disorders. *Molecular Psychiatry*, *7*(9), 985-94, 924. doi:10.1038/sj.mp.4001139

Weiner, M. F., Vobach, S., Olsson, K., Svetlik, D., & Risser, R. C. (1997). Cortisol secretion and Alzheimer's disease progression. *Biological Psychiatry*, *42*(11), 1030-1038.

Weiner, M. F., Vobach, S., Svetlik, D., & Risser, R. C. (1993). Cortisol secretion and Alzheimer's disease progression: a preliminary report. *Biological Psychiatry*, *34*(3), 158-161.

Weintraub, S., Wicklund, A. H., & Salmon, D. P. (2012). The neuropsychological profile of Alzheimer disease. *Cold Spring Harbor Perspectives in Medicine*, *2*(4), a006171. doi:10.1101/cshperspect.a006171

Weiss, E., Siedentopf, C. M., Hofer, A., Deisenhammer, E. A., Hoptman, M. J., Kremser, C. et al. (2003). Sex differences in brain activation pattern during a visuospatial cognitive task: a functional magnetic resonance imaging study in healthy volunteers. *Neuroscience Letters*, *344*(3), 169-172.

Welberg, L. (2009). Stress: Glucocorticoids in mitochondria: getting it just right. *Nature Reviews Neuroscience, 10*(4), 246-247. doi:10.1038/nrn2622

West, J., Otte, C., Geher, K., Johnson, J., & Mohr, D. C. (2004). Effects of Hatha yoga and African dance on perceived stress, affect, and salivary cortisol. *Annals of Behavioral Medicine, 28*(2), 114-118. doi:10.1207/s15324796abm2802_6

Whitfield, K. E., Kiddoe, J., Gamaldo, A., Andel, R., & Edwards, C. L. (2009). Concordance rates for cognitive impairment among older African American twins. *Alzheimer's & Dementia, 5*(3), 276-279. doi:10.1016/j.jalz.2008.09.003

Whitworth, J. A., Williamson, P. M., Mangos, G., & Kelly, J. J. (2005). Cardiovascular consequences of cortisol excess. *Vascular Health & Risk Management, 1*(4), 291-299.

Wignall, E. L., Dickson, J. M., Vaughan, P., Farrow, T. F., Wilkinson, I. D., Hunter, M. D. et al. (2004). Smaller hippocampal volume in patients with recent-onset posttraumatic stress disorder. *Biological Psychiatry, 56*(11), 832-836. doi:10.1016/j.biopsych.2004.09.015

Wilcock, D. M. (2012). A changing perspective on the role of neuroinflammation in Alzheimer's disease. *International Journal of Alzheimer's Disease, 2012*, 495243. doi:10.1155/2012/495243

Wilkosz, P. A., Seltman, H. J., Devlin, B., Weamer, E. A., Lopez, O. L., DeKosky, S. T. et al. (2010). Trajectories of cognitive decline in Alzheimer's disease. *International Psychogeriatrics, 22*(2), 281-290. doi:10.1017/S1041610209991001

Wilks, S. E. & Croom, B. (2008). Perceived stress and resilience in Alzheimer's disease caregivers: testing moderation and mediation models of social support. *Aging & Mental Health, 12*(3), 357-365. doi:10.1080/13607860801933323

Williams, S. L., Williams, D. R., Stein, D. J., Seedat, S., Jackson, P. B., & Moomal, H. (2007). Multiple traumatic events and psychological distress: the South Africa stress and health study. *Journal of Traumatic Stress, 20*(5), 845-855. doi:10.1002/jts.20252

Wilson, R. S., Beckett, L. A., Barnes, L. L., Schneider, J. A., Bach, J., Evans, D. A. et al. (2002). Individual differences in rates of change in cognitive abilities of older persons. *Psychology and Aging, 17*(2), 179-193.

Wilson, R. S., Beckett, L. A., Bennett, D. A., Albert, M. S., & Evans, D. A. (1999). Change in cognitive function in older persons from a community population: relation to age and Alzheimer disease. *Archives of Neurology, 56*(10), 1274-1279.

Wilson, R. S., Begeny, C. T., Boyle, P. A., Schneider, J. A., & Bennett, D. A. (2011). Vulnerability to stress, anxiety, and development of dementia in old age. *The American Journal of Geriatric Psychiatry, 19*(4), 327-334. doi:10.1097/JGP.0b013e31820119da

Wilson, R. S., Evans, D. A., Bienias, J. L., Mendes de Leon, C. F., Schneider, J. A., & Bennett, D. A. (2003). Proneness to psychological distress is associated with risk of Alzheimer's disease. *Neurology, 61*(11), 1479-1485.

Wilson, R. S., Hebert, L. E., Scherr, P. A., Barnes, L. L., Mendes de Leon, C. F., & Evans, D. A. (2009). Educational attainment and cognitive decline in old age. *Neurology, 72*(5), 460-465. doi:10.1212/01.wnl.0000341782.71418.6c

Wilson, R. S., Li, Y., Aggarwal, N. T., Barnes, L. L., McCann, J. J., Gilley, D. W. et al. (2004). Education and the course of cognitive decline in Alzheimer disease. *Neurology, 63*(7), 1198-1202.

Wilson, R. S., Schneider, J. A., Boyle, P. A., Arnold, S. E., Tang, Y., & Bennett, D. A. (2007). Chronic distress and incidence of mild cognitive impairment. *Neurology, 68*(24), 2085-2092. doi:10.1212/01.wnl.0000264930.97061.82

Wolf, O. T., Convit, A., McHugh, P. F., Kandil, E., Thorn, E. L., de, S. S. et al. (2001). Cortisol differentially affects memory in young and elderly men. *Behavioral Neuroscience, 115*(5), 1002-1011.

Wolf, O. T., Convit, A., Thorn, E., & de Leon, M. J. (2002). Salivary cortisol day profiles in elderly with mild cognitive impairment. *Psychoneuroendocrinology, 27*(7), 777-789.

Wolk, D. A., Zhang, Z., Boudhar, S., Clark, C. M., Pontecorvo, M. J., & Arnold, S. E. (2012). Amyloid imaging in Alzheimer's disease: comparison of florbetapir and Pittsburgh compound-B positron emission tomography. *Journal of Neurology, Neurosurgery & Psychiatry, 83*(9), 923-926. doi:10.1136/jnnp-2012-302548

Woodard, J. L., Seidenberg, M., Nielson, K. A., Smith, J. C., Antuono, P., Durgerian, S. et al. (2010). Prediction of cognitive decline in healthy older adults using fMRI. *Journal of Alzheimer's Disease, 21*(3), 871-885. doi:10.3233/JAD-2010-091693

Woods, R. P. (2003). Multitracer: a Java-based tool for anatomic delineation of grayscale volumetric images. *Neuroimage, 19*(4), 1829-1834.

Woods, B. T., Ward, K. E., & Johnson, E. H. (2005). Meta-analysis of the time-course of brain volume reduction in schizophrenia: implications for pathogenesis and early treatment. *Schizophrenia Research, 73*(2-3), 221-228.

Woodward, S. H., Kaloupek, D. G., Streeter, C. C., Kimble, M. O., Reiss, A. L., Eliez, S. et al. (2006). Hippocampal volume, PTSD, and alcoholism in combat veterans. *American Journal of Psychiatry, 163*(4), 674-681. doi:10.1176/appi.ajp.163.4.674

Wozniak, M. A., Itzhaki, R. F., Faragher, E. B., James, M. W., Ryder, S. D., & Irving, W. L. (2002). Apolipoprotein E-epsilon 4 protects against severe liver disease caused by hepatitis C virus. *Hepatology, 36*(2), 456-463. doi:10.1053/jhep.2002.34745

Wust, S., Federenko, I., Hellhammer, D. H., & Kirschbaum, C. (2000). Genetic factors, perceived chronic stress, and the free cortisol response to awakening. *Psychoneuroendocrinology*, *25*(7), 707-720.

Xing, M., Ai, Y. M., He, R. L., Gao, J. W., Song, P. P., Wang, X. C. et al. (2012). Current status and influencing factors regarding quality of life among patients with Alzheimer's disease. *Zhonghua Liuxingbingxue Zazhi*, *33*(6), 606-609.

Xu, W. L., von, S. E., Qiu, C. X., Winblad, B., & Fratiglioni, L. (2009). Uncontrolled diabetes increases the risk of Alzheimer's disease: a population-based cohort study. *Diabetologia*, *52*(6), 1031-1039. doi:10.1007/s00125-009-1323-x

Yaffe, K., Vittinghoff, E., Lindquist, K., Barnes, D., Covinsky, K. E., Neylan, T. et al. (2010). Posttraumatic stress disorder and risk of dementia among US veterans. *Archives General Psychiatry*, *67*(6), 608-613. doi:10.1001/archgenpsychiatry.2010.61

Yehuda, R. & Flory, J. D. (2007). Differentiating biological correlates of risk, PTSD, and resilience following trauma exposure. *Journal of Traumatic Stress*, *20*(4), 435-447. doi:10.1002/jts.20260

Yesavage, J. A., Brink, T. L., Rose, T. L., Lum, O., Huang, V., Adey, M. et al. (1982). Development and validation of a geriatric depression screening scale: a preliminary report. *Journal of Psychiatric Research*, *17*(1), 37-49.

Yusuf, A. J., Baiyewu, O., Sheikh, T. L., & Shehu, A. U. (2011). Prevalence of dementia and dementia subtypes among community-dwelling elderly people in northern Nigeria. *International Psychogeriatrics*, *23*(3), 379-386. doi:10.1017/S1041610210001158

Zahodne, L. B., Glymour, M. M., Sparks, C., Bontempo, D., Dixon, R. A., MacDonald, S. W. et al. (2011). Education does not slow cognitive decline with aging: 12-year evidence from the victoria longitudinal study. *Journal of the International Neuropsychological Society*, *17*(6), 1039-1046. doi:10.1017/S1355617711001044

Zautra, A. J., Affleck, G. G., Tennen, H., Reich, J. W., & Davis, M. C. (2005). Dynamic approaches to emotions and stress in everyday life: Bolger and Zuckerman reloaded with positive as well as negative affects. *Journal of Personality*, *73*(6), 1511-1538.

Zeng, Y., Hughes, C. L., Lewis, M. A., Li, J., & Zhang, F. (2011). Interactions between life stress factors and carrying the APOE4 allele adversely impact self-reported health in old adults. *Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *66*(10), 1054-1061. doi:10.1093/gerona/glr106

Zhang, G., Li, J., Purkayastha, S., Tang, Y., Zhang, H., Yin, Y. et al. (2013). Hypothalamic programming of systemic ageing involving IKK-beta, NF-kappaB and GnRH. *Nature*, *497*(7448), 211-216. doi:;10.1038/nature12143

Zhao, Z. Y., Lu, F. H., Xie, Y., Fu, Y. R., Bogdan, A., & Touitou, Y. (2003). Cortisol secretion in the elderly. Influence of age, sex and cardiovascular disease in a Chinese population. *Steroids, 68*(6), 551-555.

Appendix A

Sociodemographic Questionnaire

1. Age: _____

2. Date of Birth (d/m/y): _____

3. Sex (circle one): Male Female

4. Race (circle one): White Black Coloured
Indian Other: specify: _____

5. Handedness (circle one): Left Right Ambidextrous

6. Home Language:
_____

7. Do you speak any other languages? Please specify:
_____

8. Who was/were your primary caregiver(s) during your childhood? (E.g., parents, mother, father, grandmother, grandfather, uncle, aunt, etc.)
_____

9. Are you a caregiver? (Who do you care for?)
_____

10. What is the total monthly income of the household in which you live? If you are a student please take care to put your immediate caregivers monthly income not your own (circle one):

R0 – R499 R500 – R999 R1000 - R2499

R2500 – R5499 R5500 – R9999 R10 000+

11. What term best describes the kind of neighbourhood in which you grew up?
SUBURBAN

URBAN

TOWNSHIP

INTERMEDIATE

12. What is the name of the neighbourhood in which you grew up?

_____

_

Section A. Education

13. Education (highest degree or grade completed):

_____

14. What are the names of the schools you attended during your schooling career?

Junior school

_____

High School

_____

15. If you attended multiple schools in high school, how many months/years roughly did you spend at each and which schools were they?

_____

16. Was most of your school education completed in a rural or urban setting (circle one)?

RURAL URBAN

17. In which language was most of your school education completed?

_____

18. Did you have to repeat any grades? YES NO

If yes, please specify which grade(s):

_____

19. Did you receive a matric certificate? _____

20. If so, at which school did you complete your matric?

_____

21. Did you matriculate from a public high school or a private high school (circle one)?

PUBLIC PRIVATE

22. Roughly how many students were there per teacher in high school (that which you matriculated from)?

---

23. Did you, or are you presently, attending any tertiary education?

YES NO

If yes, what are you studying?

_____

Where are you studying?

_____

Please only answer the following questions if you currently are NOT receiving any level of education

24. Did you receive any further education post-matric? YES NO

If yes, please specify at which institution/college etc. this was received:

_____

_

25. How many years of education did you receive post-matric? _____

26. What field of study was this in? _____

27. Education (highest degree or grade completed): _____

Section B: Health

(Please circle the appropriate answer for each of the questions below)

28. Would you say your birth was: Normal Abnormal Don't know

29. Have you ever experienced a head injury? (e.g., being hit on the head with an object and losing consciousness as a result)

YES

NO

If yes, please specify:

_____

30. Have you ever been involved in a motor vehicle accident?

YES

NO

If yes, how old were you at the time?

_____

31. Have you ever had surgery? YES NO

If yes:

What type of surgery?

_____

How old were you at the time of surgery?

_____

32. Do you now, or have you ever, experienced any of the following medical conditions:

32.1. Allergies YES NO

If yes, please specify:

_____

32.2. Asthma YES NO

32.3. Tuberculosis YES NO

32.4. Hypertension (high blood pressure) YES NO

32.5. Epilepsy (i.e., seizures or fits) YES NO

32.6. Neurological problems YES NO

If yes, please specify:

_____

32.7. Depression YES NO

32.8. Treated for/ diagnosed with any memory problems or disorders

YES NO

If yes, please specify:

_____

32.9. Learning difficulties (dyslexia, ADD/ADHD) YES NO

If yes, please specify:

_____

32.10. Problems with your vision YES NO

If yes, please specify:

_____

32.11. Problems with your hearing YES NO

If yes, please specify:

_____

33. Do you have any family history of any of the above medical conditions?

YES

NO

If yes, please specify:

_____

_____

34. Are you currently taking any prescription medication(s)?

YES

NO

If yes, what medication(s)?

_____

35. Do you participant in mental activity? YES NO

36. Do you participate in physical activity? YES NO

37. Do you participant in religious activity? YES NO

Appendix B

Altered CAMCOG-R Items for Use in a South African Population

Question number	Original question	Revised question
144	Can you tell me where we are now? For instance, what county (state) are we in?	Can you tell me where we are now? For instance, what province are we in?
146	What are two main streets nearby (or near your home)?	What country are we in?
155	Was there wireless/radio in this country before television was invented?	Was there radio in this country before television was invented?
157	I am going to show you some objects. Please tell me the name of each one. Show 'Pictures for naming' in booklet. [Pictures: (1) shoe, sandal; (2) typewriter; (3) scales; (4) suitcase, portmanteau; (5) barometer; (6) table lamp; lamp]	I am going to show you some objects. Please tell me the name of each one. Show 'Pictures for naming' in booklet. [Pictures: (1) shoe, sandal; (2) screwdriver; (3) clothes iron; (4) suitcase, portmanteau; (5) clock; (6) table lamp; lamp]
164	Can you tell me what were the objects in the coloured pictures I showed you a little while ago? [Answer: (1) shoe, sandal; (2) typewriter; (3) scales; (4) suitcase, portmanteau; (5) barometer; (6) table lamp; lamp]	Can you tell me what were the objects in the coloured pictures I showed you a little while ago? [Answer: (1) shoe, sandal; (2) screwdriver; (3) clothes iron; (4) suitcase, portmanteau; (5) clock; (6) table lamp; lamp]
165	Which of these objects did I show you below? [Answer: (1) shoe, sandal; (2) screwdriver; (3) clothes iron; (4) suitcase,	Which of these objects did I show you below? [Answer: (1) shoe, sandal; (2) screwdriver; (3) clothes iron; (4) suitcase,

	portmanteau; (5) barometer; (6) table lamp; lamp]	portmanteau; (5) clock; (6) table lamp; lamp]
169	Who was the leader of the Russians in the Second World War? [Correct answer: Stalin]	Who was the Prime Minister of South Africa during the Second World War? [Correct answer: Jan Smuts]
170	What was Mae West famous for? [Correct answer: Entertainer, Film Star, life jacket]	What was Louis Armstrong famous for? [Correct Answer: Singer, Saxophonist, Jazz Singer]
171	Who was the famous flyer whose son was kidnapped? [Correct answer: Lindbergh]	Which famous film, starring Vivien Leigh and Clark Gable was released in the 1930s? [Correct answer: Gone with the Wind]
166a	Who was the US President who was shot in Texas? [Correct answer: John F. Kennedy]	What is the name of the South African prime minister who was stabbed in parliament? [Correct answer: Hendrik Verwoed]
167a	What is Yoko Ono famous for? [Correct Answer: Wife of Beatle, John Lennon]	What is Steve Biko famous for? [Correct answer: Black activist, died in police custody]
169a	What was Edmund Hilary famous for? [Correct answer: First to reach summit of Mt Everest]	Who was the first South African to win a Nobel Peace Prize? [Correct answer: Albert Luthuli]
170a	Who was the first woman Prime Minister of India? [Correct answer: Indira Ghandi]	Who was the first surgeon to perform a heart transplant? [Correct answer: Christiaan (Chris) Barnard]
171a	Who was the famous cinema	Which island off the coast of

	actress who married Prince Rainier of Monaco? [Correct Answer: Grace Kelly]	South Africa was used as a leper colony, military base and prison? [Correct answer: Robben Island]
172	What is the name of the present King or Queen?	What is the name of the present President of South Africa?
173	Who is likely to be the next King or Queen?	What was the full date when two planes flew into the Twin Towers in New York? [Correct answer: 11 September 2001]
174	What is the name of the Prime Minister?	Who is the president of USA?
176	Name the following three objects taking one second to say each: apple, table, penny.	Name the following three objects taking one second to say each: apple, table, pen.
180	What were the three objects I asked you to repeat a little while ago? [Correct answer: apple, table penny]	What were the three objects I asked you to repeat a little while ago? [Correct answer: apple, table pen]
190	Write this name and address on the envelope: Mr. John Brown 42 West Street, Bedford	Write this name and address on the envelope: Mr. John Brown 42 West Street, Bellville
195	If someone went shopping and was given 15 pence as change from £1, how much did they spend?	If some went shopping and was given 15 cents as change from R1, how much did they spend?
201	Who is this? [Show picture of (1) Queen; (2) Pope, Archbishop, Bishop]	Who is this? [Show picture: (1) Archbishop Desmond Tutu; (2) Nelson

		Mandela]
203	Can you tell me who this is, or what he/she does? [Indicate any two people Available]	Can you tell me who this is, or what he/she does? [Turn to the last section of the CAMCOG picture booklet and show any two pictures of people in service professions: policeman, doctor, nurse, fireman, priest]

Appendix C

Participation Information Leaflet and Consent Form

TITLE OF THE RESEARCH PROJECT: Risk factors for the development of cognitive
impairment in the elderly

PROTOCOL NUMBER:

PRINCIPAL INVESTIGATOR: Dr Marc I Combrinck

ADDRESS: Divisions of Neurology and Geriatric Medicine, Department of Medicine, E7 Room 63, Groote Schuur Hospital, Private Bag X3, Observatory, Cape 7935

CONTACT NUMBER: +27 21 404 3198 or 404 3120

We are inviting you to participate in a research project. Please take some time to read the information presented here. It explains the details of the project. If there are any aspects of the project you do not understand, please do not hesitate to ask the study staff or doctor. It is important that you are fully satisfied that you clearly understand what this research entails and how you could be involved. Your participation in the study is entirely voluntary and you are free to decline to participate. If you say no, this will not affect you negatively in any way whatsoever. It will not affect any future medical treatment you may need. You are also free to withdraw from the study at any point, even if you did initially agree to take part. You do not have to give a reason for withdrawing.

This study has been approved by the Research Ethics Committee of the Faculty of Health Sciences of the University of Cape Town. It will be conducted according to the ethical guidelines and principles of the International Declaration of Helsinki, the South African Guidelines for Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research.

This trial is being run by the Division of Neurology and the Institute of Ageing in Africa in the Department of Medicine at the University of Cape Town. We aim to recruit a total of 150 participants over a period of 3 years.

What is this research study all about?

Some people develop memory problems as they get older. Many elderly people have mild memory difficulties. However, in a few, the problem may be more severe. We are interested in finding out more about what causes the difficulties with memory and other higher brain functions. In order to do so, we should like to investigate these possible causes using a number of methods. These include blood tests, questions you would need

to answer about yourself, tests of memory and other higher brain functions, a CT scan of the brain, and tests of your saliva. In some instances we may, with your special permission, perform tests on the fluid covering your brain and spine by doing a lumbar puncture. We shall also ask some of you to undergo a special scan known as an MRI at our research facility at Tygerberg Hospital.

We are interested in testing people both with memory difficulties and those without, so that we can compare the two groups. In this way we might be able to identify causes of memory impairment. Our research findings may help to prevent, or to better diagnose and treat, these conditions in the future.

Procedures

If you agree to take part in the study and you meet all the conditions required to enter the study, you will be invited to visit our clinic on two separate days. At these visits to our clinic we shall:

(1) take a detailed history.
(2) interview your relative/friend (someone who knows you well) to find out whether he/she thinks you have any memory difficulties.
(3) perform a full physical examination. This will include measuring your blood pressure, listening to your heart and chest, examining the nervous system and testing your urine.
(4) take approximately 36 ml (7 tablespoons) of blood to look for possible causes of memory impairment. These will include:

(i) a blood sugar (glucose) (for diabetes)
(ii) a blood cholesterol level
(iii)tests of liver, kidney and thyroid gland function
(iv)haemoglobin, blood cell counts
(v) tests for vitamins or vitamin deficiencies (vitamin B-12 and homocysteine)
(vi)a test for syphilis. (This test is routinely performed in hospital clinics because syphilis used to be a common cause of impairment of higher brain function in the past)
(vii) a sample to measure inflammation in the blood (cytokines)

(viii) one sample will be used to prepare DNA from your blood. We shall test this for a gene called apolipoprotein E (APOE). Some forms of this gene may be associated with a higher risk of developing memory problems. However, this test does not diagnose that you have, or will necessarily develop, memory problems. We are doing it purely for research; it may help us to better understand some causes of memory difficulties.

(ix)A test for a chemical in the blood known as clusterin. This chemical may be increased in people with memory difficulties.

(5) We shall ask you to complete questionnaires about yourself and we shall perform tests of your memory and other higher mental functions. These will be conducted in a quiet, relaxed atmosphere. We expect that these tests will be of about two hours' duration. However, there will be opportunities to rest in-between tests.

(6) We shall perform a MRI scan of the brain. This is a special X-ray photograph that will show us the structure of your brain. It can detect lumps or masses inside the head and it might also give us some idea about brain shrinkage. It will also show any obvious strokes that you might have had. If you like, we shall show you the pictures of your brain scan.

(7) In some instances we may wish to perform a lumbar puncture to obtain a sample of the fluid (the cerebrospinal fluid or CSF) that surrounds the brain and the spinal cord. We shall only perform this test with your special permission and if we think the test will help diagnose and treat the cause of your memory problems. We shall send the sample to the laboratory to test for infection or inflammation. We shall also store a sample in the freezer to be analysed at a later stage for chemicals related to inflammation (cytokines).

If we think a lumbar puncture is necessary and if you agree, the test will be performed in our Neurology Ward at the Groote Schuur Hospital. You will need to rest in bed, lying flat, for a couple of hours afterwards. The test is usually well tolerated, especially in elderly people, and there are usually no side-effects. Occasionally some people develop headaches after the test, often a day or two later. We generally advise people to have a restful two days after the procedure and to drink plenty of fluids. Should headaches occur, they are usually relieved by lying down flat and taking simple pain-killers like paracetamol. Very rarely, some people (usually young adults) develop quite bad headaches and for this we may need to re-admit you to our hospital ward for pain relief. We shall telephone all participants a day or two after the lumbar puncture to make sure they are okay.

(8) We shall measure the levels of a stress hormone, cortisol, in your saliva ("spit"). You or your relative will be asked to swab a sample of your saliva on three consecutive mornings at 09h00 a.m. We shall provide the swabs and the containers as well as clear instructions about how to collect and store the samples. The samples need to be kept refrigerated and one of the staff of our study group will collect them from you.

If we find any abnormal results that we think will need further treatment, we shall contact you. With your permission, we shall refer you to the appropriate health services. For example, we may diagnose hypertension or diabetes mellitus for the first time. If we find that you or your relative/friend has a significant memory problem that is interfering with your daily living activities, we shall refer you to a Memory Clinic. Your permission will always be sought first.

(9) Some participants in the study will be asked to undergo a special type of brain scan which will be performed at the Cape Universities Brain Imaging Centre (CUBIC) at Tygerberg Hospital. This scan is called an MRI (magnetic resonance imaging) scan. It provides a detailed picture of the brain including the parts involved in memory. We are also able to measure chemicals in parts of the brain using what's known as magnetic resonance spectroscopy (MRS).

We shall provide transport for you to the facility at Tygerberg Hospital where necessary. On arrival we shall ask you and your relative questions regarding the following: whether you have had a cardiac pacemaker, a neuro-stimulator, previous eye injuries or a foreign body, previous neurosurgery, previous other surgery involving metal implants, a cochlear implant, whether you have been a welder or metal grinder and whether you are claustrophobic or not. The scan will require you to lie on your back on a table that will move into the scanning machine for the 30 to 40 minutes it will take for the scan to be completed.

During this time you will be able to close your eyes and rest. You will also be able to talk to the study doctor/assistant at all times during the scan should you experience any discomfort. The scan is a safe procedure if you have been screened correctly for the presence of any magnetic material on or inside your body. As the scan is done in a relatively confined space, occasionally some people become anxious. This does not happen often, and if you feel anxious beforehand, we will spend time allowing you to get used to the surroundings before we begin. When the magnet in the machine is switched on, it will make some loud banging noises, but you will be clearly warned when this will take place. At this time you will feel nothing and the noise is not harmful to you in any way. To minimise the possible discomfort associated with this, we will give you some soft earplugs and will also put earphones on so that you can listen to music if you so choose.

After the two baseline visits and the three collections of saliva, we would like to re-assess your memory functions again at one, two and three years later, respectively, provided you continue to consent to participation in the study.

What will your responsibilities be?

You will be required to attend the study visit at the appropriate time and to participate as fully as you can with the tests and questionnaires. You should answer the questions as fully and honestly as you can. If there are any questions that you cannot, or do not wish to answer, you should tell us so.

Will you benefit from taking part in this study?

You will receive little direct benefit from the study.
However, you will undergo a thorough medical check-up as part of the research protocol. As previously indicated, we shall, with your permission, refer you to the appropriate medical services if any treatable abnormalities are found.

Are there any risks in your taking part in this research?

You may feel uncomfortable about answering some of the questions about yourself or your friend/relative. Some people don't like talking, or knowing about, problems related to memory or thinking. You should feel free to mention your feelings or concerns to any member of the study team.

If you do not agree to take part, what alternatives do you have?

You are free not to participate in the study or to refuse parts of the study.

Who will have access to your medical records?

The information collected about you will be treated as confidential and protected. If it is used in a publication or thesis, your identity will remain anonymous. Only the direct study team will have full access to the information. If we need to refer you to a clinic for treatment, we will provide them with the relevant information needed to treat your condition.

Will you be paid to take part in this study and are there any costs involved?

You will not be paid to take part in the study but your transport costs will be covered for the study visit. You will be re-imbursed for the sum of R150-00. There will be no costs involved for you, if you do take part.

Is there anything else that you should know or do?

- You should inform your family practitioner or usual doctor that you are taking part in a research study.
- You can contact Dr Marc Combrinck at tel (021) 404 3198 or 404 3120 if you have any further queries or encounter any problems.
- You can contact the Research Ethics Committee of the Health Sciences Faculty of the University of Cape Town 021-4066338 if you have any concerns or complaints that have not been adequately addressed by your study doctor.
- You will receive a copy of this information and consent form for your own records.

Declaration by participant and/or friend/relative/guardian

By signing below, I ……..……., hereby agree to take part in the research study entitled: "Risk Factors for Cognitive Impairment in the Elderly"

I declare that:

- I have read or had read to me this information and consent form and it is written in a language with which I am fluent and comfortable.

- I have had a chance to ask questions and all my questions have been adequately answered.
- I understand that taking part in this study is **voluntary** and I have not been pressurised to take part.
- I may choose to leave the study at any time and will not be penalised or prejudiced in any way.
- I may be asked to leave the study before it has finished, if the study doctor or researcher feels it is in my best interests, or if I do not follow the study plan, as agreed to.

Signed at (*place*) .....…..…….. on (*date*) ……...…….. 2012.

.....	.....
Signature of participant	**Signature of witness**
.....	.....
Signature of relative/friend/guardian	**Signature of witness**

- If the study doctor considers that I or my friend/relative should undergo a lumbar puncture, I shall agree to the test:

YES ☐ NO ☐

(Tick whichever box is appropriate)

- I agree to undergo an MRI scan at Tygerberg Hospital

YES ☐ NO ☐

(Tick whichever box is appropriate)

Declaration by investigator

I *(name)* ……..…… declare that:

- I explained the information in this document to ……..
- I encouraged him/her to ask questions and took adequate time to answer them.
- I am satisfied that he/she adequately understands all aspects of the research, as discussed above
- I did/did not use an interpreter. (*If an interpreter is used then the interpreter must sign the declaration below).*

Signed at (*place*) .....…..…….. on (*date*) ……...…….. 2012.

....

Signature of investigator **Signature of witness**

Declaration by interpreter

I *(name)* ……..…… declare that:

- I assisted the investigator (*name*) ……. to explain the information in this document to (*name of participant*) ……..…….. using the language medium of Afrikaans / Xhosa *(delete whichever is not applicable).*
- We encouraged him/her to ask questions and took adequate time to answer them.
- I conveyed a factually correct version of what was related to me.
- I am satisfied that the participant fully understands the content of this informed consent document and has had all his/her question satisfactorily answered.

Signed at (*place*) .....…..…….. on (*date*) ……...……...

....

Signature of interpreter **Signature of witness**

Appendix D

Salivette Instructions

Thank you again for agreeing to participate in this study. The following are the instructions for submitting 2 saliva samples, 2 consecutive days in a row at 9:00AM.

12 hours before collecting a sample, the participant must not:

1. Drink any alcohol/smoke cigarettes
2. Have any dairy products, e.g., cheese, yoghurt, milk
3. Have any fizzy drinks, oranges, lemons, pineapples (no citrus), sweets, chocolates
4. Ingest or inhale any steroids, e.g., prednisone, prednisolone, methylprednisolone

When taking the sample at 9:00AM:

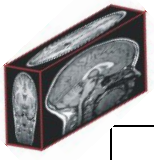
1. Make sure you have had breakfast by 7:30AM or otherwise only have breakfast after you have taken your sample i.e. after 9:00AM.
   (It is sometimes easier to avoid eating or drinking anything other than water before taking the sample).
2. Wash out your mouth with water 10 minutes before taking the sample.
3. Remove the saliva "sponge" collection device from container and chew on it for a minute.
4. Place the sponge back in the container and make sure it is tightly closed/sealed.
5. Place in freezer
6. Once your sample has been taken you may eat or drink anything you wish

After you have taken the sample:

1. If both samples are collected please call Katharine James for collection: 021 404 7750

Appendix E

MRI Volunteer Screening Form and Consent



Cape Universities Brain Imaging Centre (CUBIC)

Volunteer Information:

Name	Contact number
Date of Birth	Project name
Weight	Principle investigator

The following information is very important to ensure your safety and to prevent any interference during the MR procedure.

Please answer the following questions (mark with an X):	**Yes**	**No**	**Don't know**
Pacemaker			
Aneurism clips			
Artificial heart valve			
Vena cava filter			
Prosthesis (e.g. eye, breast etc.)			
Shrapnel in eye or body			
Neurostimulator			
Cochlear implant (ear) or hearing aid			
? Diabetic			
? Renal impairment			
? Asthma			
? Allergies			
? Any other implants (e.g. screws, plates, joint replacements)			
? Pregnant			
? Previous MRI investigation with intravenous contrast			
Is there any other device implanted or are there any other ailments that you think that we should be aware of?			

I hereby acknowledge that the potential risks of the examination have been explained to me and that during the course of the investigation it may be necessary for the intravenous injection of a contrast agent.

Attention: It is the policy of this institution not to discuss results of the MR investigation with the patients for ethical reasons. All enquiries in this regard should be directed to the referring physician.

Signature: **Date:**

Appendix F

Preliminary Results for the Structural Equation Model

Table F1 shows the results from the preliminary analyses that were explored in the SEM. The outcome variable was cognition which was further divided into Cognition Affected and Cognition Unaffected groups. These groups refer to the sum of scores from domains of cognition, as measured by the CAMCOG-R, which one would expect to be associated with mild to moderate AD (Memory, Orientation, Language), and those domains one would not expect to be affected in mild to moderate AD (Attention, Calculation, Praxis, Abstract Thinking, and Perception). As can be seen in this table, several variables were strongly correlated with both Cognition Affected and Cognition Unaffected.

Table F1
Correlations: Cognition affected and cognition unaffected with age, education, APOE-є4, cortisol, psychosocial stress, and resilience at Baseline (N = 115)

	Group	
Variable	Cognition Affected	Cognition Unaffected
Age	-.33***	-.36***
Education	.52***	.59***
APOE-є4	-.21*	-.21*
Cortisol	-.06	-.06
PSS	-.18	-.11
Resilience	.41***	.33***

Note. Values presented are for Pearson's *r*. The variables *Age* and *Education* are measured in years. APOE-є4 = apolipoprotein є4; Cortisol = log transformed values. PSS = Perceived Stress Scale – measure of psychosocial stress; CD-RISC = Connor-Davidson Resilience Scale – measure of resilience.
*p < .05. **p < .01. ***p < .001.