STRUCTURAL BRAIN MRI IN LATE LIFE
WITH A SPECIAL FOCUS ON THE OLDEST OLD

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People over the age 85, the oldest old, are the fastest growing segment of the population globally, with a substantial proportion developing dementia. Research into dementia in this age group is of public health importance, and absence of dementia could serve as a model of successful ageing. Neuroimaging studies of dementia in the 85-plus population are scarce. The aim of this thesis was to characterise the structural magnetic resonance imaging (MRI) profiles of brains with and without cognitive impairment in late life, with a special focus on the oldest old. A combined cohort aged 71 to 103 years from the Sydney Centenarian Study and Sydney Memory and Ageing Study comprised the sample. MRI-derived brain measures, including brain atrophy indices, white matter hyperintensities (WMHs) and brain infarcts, were examined by cognitive categories. The principal findings were as follows: first, in non-demented participants, a linear negative relationship was observed between age and grey matter volume, which continued into the 10^{th} and 11^{th} decades of life, with the greatest effects of age being on the medial temporal lobe and the parietal and occipital cortices. Second, thinner cortex and smaller hippocampus were strong indicators of dementia at all ages, as were deep WMHs and brain infarcts (≥ 2) at 80 but not at 95 years. Using a composite MRI pathology index, the association between structural MRI and dementia was much stronger at 80 than at 95 years. Brain vascular injuries were common at advanced age, irrespective of the cognitive status of the individual. Third, structural MRI could distinguish amnestic mild cognitive impairment (MCI), but not non-amnestic MCI, from normal individuals from 71 to 103 years. However, the MRI markers that were most indicative of amnestic MCI differed in the young old from the oldest old. This research is the first to extend our understanding of brain ageing on structural MRI into the 10^{th} and 11^{th} decades of life. MRI markers of dementia and amnestic MCI at advanced age could potentially assist in the early diagnosis of dementia and have implications for understanding the mechanisms of brain resilience in the oldest old.

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ABSTRACT

People over the age 85, the oldest old, are the fastest growing segment of the population globally, with a substantial proportion developing dementia. Research into dementia in this age group is of public health importance, and absence of dementia could serve as a model of successful ageing. Neuroimaging studies of dementia in the 85-plus population are scarce. The aim of this thesis was to characterise the structural magnetic resonance imaging (MRI) profiles of brains with and without cognitive impairment in late life, with a special focus on the oldest old. A combined cohort aged 71 to 103 years from the Sydney Centenarian Study and Sydney Memory and Ageing Study comprised the sample. MRI-derived brain measures, including brain atrophy indices, white matter hyperintensities (WMHs) and brain infarcts, were examined by cognitive categories. The principal findings were as follows: first, in non-demented participants, a linear negative relationship was observed between age and grey matter volume, which continued into the 10^{th} and 11^{th} decades of life, with the greatest effects of age being on the medial temporal lobe and the parietal and occipital cortices. Second, thinner cortex and smaller hippocampus were strong indicators of dementia at all ages, as were deep WMHs and brain infarcts (≥ 2) at 80 but not at 95 years. Using a composite MRI pathology index, the association between structural MRI and dementia was much stronger at 80 than at 95 years. Brain vascular injuries were common at advanced age, irrespective of the cognitive status of the individual. Third, structural MRI could distinguish amnestic mild cognitive impairment (MCI), but not non-amnestic MCI, from normal individuals from 71 to 103 years. However, the MRI markers that were most indicative of amnestic MCI differed in the young old from the oldest old. This research is the first to extend our understanding of brain ageing on structural MRI into the 10^{th} and 11^{th} decades of life. MRI markers of dementia and amnestic MCI at advanced age could potentially assist in the early diagnosis of dementia and have implications for understanding the mechanisms of brain resilience in the oldest old.

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DECLARATION OF CONTRIBUTIONS TO PUBLICATIONS

This thesis comprised a review paper (Chapter 2) and three data-based studies (Chapters 3, 4 and 5). I am the first author of all these papers. My contributions in each paper was more than 50%, and included: concept development, study design, data collection and management, statistical analyses, writing of drafts, responding to reviewers' comments, revision of manuscript, and preparation of the final manuscript.

Contributions of Co-Authors

For Chapter 2, the concept was developed after discussions with Perminder S. Sachdev, who together with Melissa J. Slavin, reviewed and revised the draft.

The study concept and design in Chapter 3, 4 and 5 were developed after discussions with Perminder S. Sachdev. Statistical analysis was conducted with advice from John D. Crawford. Wei Wen and Jiyang Jiang assisted in acquisition and interpretation of neuroimaging data. Laughlin Dawes assisted in identification of MRI-defined brain infarcts (Chapter 4). Perminder S. Sachdev, Henry Brodaty and Robyn L. Richmond supervised the projects. Simone Reppermund, Melissa J. Slavin, Nicole A. Kochan and Charlene Levitan co-ordinated the studies, and supervised the collection and cleaning of the clinical data. Perminder S. Sachdev, Henry Brodaty, and Nicole A. Kochan critically reviewed the manuscripts.

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ABBREVIATIONS

ACE-R	Addenbrooke's Cognitive Examination Revised
AD	Alzheimer’s disease
AGD	argyrophilic grain disease
aMCI	amnestic mild cognitive impairment
ANOVA	analysis of variance
APOE	apolipoprotein E
BADLs	Bayer activities of daily living scale
CAA	cerebral amyloid angiopathy
DLB	dementia with Lewy bodies
DMN	default mode network
DSM	Diagnostic and Statistical Manual
eTIV	estimated intracranial volume
GM	grey matter
HS	hippocampal sclerosis
IADLs	instrumental activities of daily living
ICD	International Classification of Disease
IQ CODE	Informant Questionnaire on Cognitive Decline in the Elderly
LRP	Lewy-related pathology
MAS	Memory and Ageing Study
MCI	mild cognitive impairment
MMSE	mini-mental status examination
MRI	magnetic resonance imaging
naMCI	non-amnestic mild cognitive impairment

NeuRA	Neuroscience Research Australia
OO	oldest old
PET	positron emission tomography
ROIs	regions of interest
SD	standard deviation
SE	standard error
SCS	Sydney Centenarian Study
TDP-43	43-kDa transactive response sequence DNA-binding protein
VCI	vascular cognitive impairment
WM	white matter
WMHs	white matter hyperintensities
YO	young old

CHAPTER 1: INTRODUCTION

The oldest old, variously defined as those aged 85, 88 or 90 years and over, are the fastest growing segment of the population globally [1]. Prevalence of dementia increases steadily with advancing age [2, 3], and is estimated to be approximately 25-50% in nonagenarians and 42-76% in centenarians [4] in population-based samples. Research on dementia in the very old is therefore important for population health and service planning, and absence of dementia in exceptional longevity may provide insight into successful cognitive ageing.

Both ageing and dementia are associated with progressive brain atrophy and an accumulation of brain vascular injuries [5, 6]. In the relatively young elderly (< 85 years), structural magnetic resonance imaging (MRI) has been a powerful tool to distinguish dementia processes from normal brain ageing and infer the potential neuropathological aetiologies, based on the topographic distribution and the severity of brain atrophy and vascular injuries [5, 7, 8]. However, these findings in the "young" elderly may not apply to the very old (≥ 85 years), as the neuropathological substrate of dementia is found to change with advancing age [4], and because MRI-derived brain measures are closely related to the neurobiological underpinnings of ageing and dementia [9]. So far, few structural MRI studies have focused on the 85-plus population. It remains unknown how normal brain ageing continues into the 10^{th} and 11^{th} decades of life, and which brain MRI markers could best distinguish those cognitively impaired from normal individuals at advanced ages.

In this thesis, the oldest old are defined as individuals aged 85 years or older. It is the objective of this thesis to characterise the structural MRI profiles of the brains with and without cognitive impairment in late life, with a special focus on the oldest old.

1.1 The ageing population and the oldest old

The ageing of the world's population is expected to accelerate over the next 35 years, with the 60-plus population estimated to double from the current 12% to 22% by 2050 [10]. In Australia, the age group of 65 years and over is projected to increase from 3.2 million in June 2012 to between 9.0 and 11.1 million by 2061, thereby comprising approximately 23.5% of the population [11]. Such growth has particular implications for health and social services, as ageing is accompanied by increasing prevalence of age-related diseases, impaired functioning and disability [12].

Individuals reaching the age of 85 and older have become the fastest growing population in many industrialised countries, including Australia, the United States, Canada, Japan and Europe [13-15]. In Australia, the age group of 85 years and over is projected to increase from approximately 0.4 million in June 2012 to 3.5 million by 2069, which will account for approximately 4.5% of the Australian population in 50 years [11]. In the United States, individuals aged 90 and above are estimated to increase from the current two million to as many as 10 million by 2050 [14]. Worldwide, centenarians are expected to reach as many as 2.2 million by 2050, which is a 15-fold increase on the current estimates [16].

Despite the dramatic growth in the number of long-lived individuals, this segment of the population is under-examined, and the heterogeneity in their health patterns is often overlooked. In a large population-based cohort (60- plus N = 3080, 90-plus N = 486), the median number of age-related morbidities was approximately 3, and the median

score of mini-mental status examination (MMSE) was 21 at the age of 95 years [12], which suggests worse physical and cognitive functioning in nonagenarians compared to septuagenarians and octogenarians. Meanwhile, some individuals of 90 years and over have shown considerable "compression of morbidity" compared to younger elderly, that is, the older age the later onset and shorter duration of illness towards the end of lifespan [17, 18]. Approximately 15-25% of the centenarians are considered as cognitively intact [19], and some exceptional cases have been reported as being both cognitively and physically healthy [20], suggesting that dementia and disability are not inevitable even if an individual lives long enough. Thus, research into longevity not only helps with service planning, it could also provide insight into successful ageing.

Although physical decline and disability are increasingly recognised after the age of 85 years [12], brain and cognitive ageing beyond this point remain under-explored. Therefore, this thesis aims to address the knowledge gap of cognitive dysfunction and structural MRI profiles of aged brains, with a special focus on the oldest old population.

1.2 Dementia in the ageing population

In 2008, the World Health Organization (WHO) declared dementia as a public health priority, due to the growing prevalence and the substantial cost in providing health and social care. The latter was estimated to be more than USD600 billion per year worldwide [21]. Therefore, it is essential to improve early diagnosis and better understand the extent and the nature of this syndrome, so as to ameliorate management.

1.2.1 Diagnosis of dementia

Dementia is defined as a syndrome characterised by a decline in cognitive function from a premorbid level that is sufficiently severe to result in impaired functioning in daily activities and thereby loss of independent functioning [22]. Multiple operational criteria

for diagnosing dementia exist, including those proposed in the Diagnostic and Statistical Manual of Mental Disorder (DSM) and International Classification of Disease (ICD), as summarised in Table 1.1.

The choice of diagnostic criteria has a substantial impact on the detection of dementia. In the Canadian Study of Health and Aging, a cohort of 1879 individuals aged 65 years and over, the dementia prevalence was much higher using DSM-III-R and DSM-IV criteria (17.3% and 13.7% respectively) compared with ICD-based criteria (5.0% by ICD-9 and 3.1% by ICD-10) [23]. Such variance could be ascribed to the ICD's criterion of impaired executive function and 6-month duration of symptoms, making it difficult to identify dementia in the early stages. Since the rate of cognitive decline increases with advancing age, the diagnosis criteria used should be particularly considered for the very old, and it would appear that the DSM-based criteria may identify dementia in earlier stages than the ICD-based criteria.

Diagnosing dementia in the oldest old is challenging for a number of other reasons [1]. First, instead of a 3-hour neuropsychological assessment, a shortened cognitive test battery is usually implemented due to frailty and an inability to tolerate an extensive assessment at this age [15, 24]. Information obtained is somewhat limited compared to an extended assessment. Second, there is a lack of normative data to determine cognitive impairment beyond the age of 90 years, and the available norms are often based on small sample size [24]. Third, medical comorbidities and sensory impairment are widely prevalent in this age group, which invariably interfere with cognitive performance [25]. These practical difficulties result in additional variance in detecting dementia in the oldest old and should be considered when interpreting the epidemiology data.

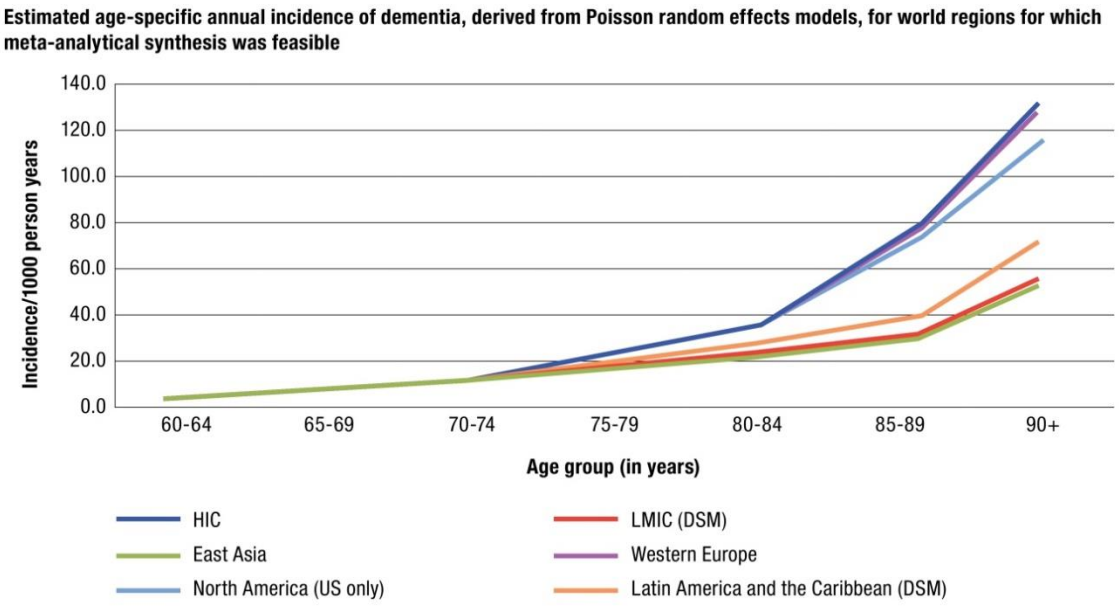
Table 1.1 Diagnosis criteria for dementia in the Diagnostic and Statistical Manual of Mental Disorders (DSM) and International Classification of Disease (ICD) systems.

Cognitive domains that could be affected in dementia	DSM-III-R (1987)	DSM-IV (1994)	DSM-5 (2013)	ICD-9 (1978)	ICD-10 (1993)
Memory		X	O		
Short-term (learning)	X			X	X
Long-term	X				
Executive function		O	O		
Abstract thinking	O			X	X
Judgement	O			X	X
Problem solving				X	X
Complex attention	O		O		
Language	O	O	O		
Perceptual-motor function	O	O	O		
Social cognition					
Recognition of emotions			O		
Theory of mind			O		
Insight			O		
Personality	O				
Functioning					
Work	+	+		+	
Social activities	+	+		+	
Independence in activities of daily living			X		X
Relationships with others	+				
Other features					
Decline from a premorbid level	X	X	X	X	X
Symptoms ≥ 6 months				X	X
Normal consciousness	X	X		X	X
Cannot explained by another mental disorder			X		

"X": impairment in the domain is always required for diagnosis; "O" or "+": one or more within the same symbols is required for diagnosis.

1.2.2 Epidemiology of dementia

According to the World Alzheimer Report 2015, the prevalence of dementia, mostly based on DSM-IV or DSM-III-R criteria, is estimated to triple every 10 years, being 1.8% at ages of 60-64 years, 4.5% at 70-74, 12.5% at 80-84 and 38.3% in the age group of 90-plus in the Australasian region [26]. Similarly, as shown in Figure 1.1, the worldwide incidence of dementia increases exponentially with advancing age, from 3.9 per 1000 person years globally in the age range 60-64 years to 53.1 per 1000 person in the age range 85-89 years and 104.8 per 1000 person years in the 90-plus population [26].



Adapted by permission from the Alzheimer's Disease International. World Alzheimer Report 2015. London: Alzheimer's Disease International; 2015.

Figure 1.1 Estimated age-specific annual incidence of dementia.

Data on dementia in the 90-plus population are however limited. Most studies combined individuals of 90-plus into one age category, thus obtaining rates of dementia within a narrower age range (e.g. 90-94, 95-99 and 100-plus) was not always possible. For only a handful of studies that had stratified age, large variance in the prevalence of dementia

was noted, ranging from 22.0% to 76.3% in nonagenarians [27, 28], and 27% to 100% in centenarians [29]. In addition to the diverse diagnosis criteria, factors such as size and representativeness of the sample [15] and different instruments used [30] in cognitive assessment also contribute to the source of the variance observed. These factors need to be accounted for to achieve a better understanding of dementia in the 90-plus population.

1.2.3 Neuropathological substrate of dementia

Late-onset dementia (after the age of 65) could result from a wide range of aetiologies, alone or in combination. In the young old (< 85), the most notable pathologies underlying dementia are Alzheimer's disease (AD) pathology, vascular pathology and a combination of the two [31]. Other common pathologies, such as Lewy-related pathology (LRP), cerebral amyloid angiopathy (CAA), other neurodegenerative proteinopathies and their varying combinations are considered to account for less than one third of the dementia cases in this age group [32].

In the oldest old, pathological underpinnings of dementia are thought to be somewhat different from that in young old. Common neuropathologies, as mentioned above, are found to be prevalent in both cognitively intact and impaired individuals. In addition, pathologies that are relatively rare in the young old, such as hippocampal sclerosis (HS) of ageing [33], argyrophilic grain disease (AGD) [34] and primary age-related tauopathy [35], are found to be prevalent in the very old. Possibly due to these factors, conventional pathological correlates of dementia in the young old, such as AD pathology alone [27] or in combination with vascular pathology [36], are weak indicators of dementia in nonagenarians and centenarians. A recent study taking account of 8 different types of pathological measures (AD pathology, HS, CAA, LBD, micro- and macro-infarcts, white matter disease and other), reported that mixed pathology is

the main contributor to dementia in the 90-plus age group [37], suggesting the pathogenesis of dementia at advanced age is multifactorial rather than being determined by one predominant pathology.

Taken together, precision is warranted in understanding the prevalence and aetiology of dementia in the oldest old. Chapter 2 of this thesis aimed to summarise the epidemiology, pathogenesis, and risk and protective factors of dementia in the oldest old, by reviewing high-quality, population-based studies of dementia in subjects of 90-plus years. A discussion of challenges and limitations of such studies has also been included.

1.3 Mild cognitive impairment (MCI)

MCI is a term used to designate an early, but abnormal state of cognitive functioning that is not sufficiently severe to cause dementia [38]. The original criteria of MCI were proposed in 1999, emphasising mild memory impairment as a prodromal sign of AD dementia [39]. Subsequently, this concept had been broadened to include any of the cognitive domains, in an attempt to capture the prodromal stages of a variety of dementias [38, 40].

1.3.1 Diagnosis of MCI

In 2004, the International MCI Working Group proposed criteria for diagnosing MCI, which included: 1) the individual is neither normal nor demented; 2) self or informant report and impairment on objective cognitive tasks, and/or, there is evidence of cognitive decline over time on objective cognitive tasks; and 3) basic activities of daily living are preserved, and the complex instrumental functions are either intact or minimally impaired [40]. Further, four subtypes of MCIs were defined based on clinical presentations, that is, whether memory is impaired (amnestic vs. non-amnestic) and

whether multiple cognitive domains are affected (single-domain vs. multi-domain) [38, 40].

The diagnosis of MCI has generally not been used in the oldest old, although most studies did note that participants often had mild levels of cognitive impairment [4]. As normal ageing per se is associated with progressive cognitive decline, it is not unexpected to have mild impairment when an individual lives long enough [41, 42]. Therefore, a "mild" level of cognitive impairment is commonplace and sometimes considered as "normative" in this age group, in particular for those nonagenarians and centenarians.

From a practical stand point, judgement of "normal" or MCI is not fully reliable in the 90-plus population. So far, only the 90+ Study in the United States has classified individuals into aMCI and naMCI, yet this was based on a shortened neuropsychological assessment, and their normative data were derived from non-demented (but not normal cognition) individuals [24, 43]. "Normal" cognition was reported to be approximately 1 in 3 in nonagenarians and 1 in 4 in centenarians [4] based on different parameters across studies, such as the clinician's mental state examination (blinded to neuropsychological tests on cognitive domains) [24], neuropsychological test performance within a particular range and functional independence in daily activities [30, 44]. Yet there is no consensus on the criteria of normal cognition or MCI at advanced age, and its classification is not always comparable to that of the young old. This needs to be accounted for when comparing across age groups.

1.3.2 Epidemiology of MCI

Prevalence of MCI in the general elderly population (aged 60-95 years) varies between 3.2% and 42% in published studies [45-47]. Single-domain MCIs are generally more common than multidomain MCIs [48-50]; and the amnestic MCI (aMCIs) as frequent as non-amnestic MCI (naMCIs) [51]. The considerable discrepancies in prevalence across studies are thought to be driven by the varying source of participants, different neuropsychological tests and normative data applied as well as differences in the operational definition of cognitive impairment [45].

The relationship of MCI prevalence with age is weak [45, 47], with only a few studies reporting slightly higher rates in older age groups (43.3% in 80-90 years versus 36.7% in 70 -79 years) [46]. This is different from dementia, where prevalence rates triple for every increased age decade [22].

In the age group 60-90 years, MCI is associated with an increased risk of progressing to dementia [48, 51, 52]. The risk is found to be particularly high for older individuals [50, 53], and for those with multi-domain amnestic MCI subtype [48, 51]. However, not all MCI individuals convert to dementia; population-based studies reported that 28.3% to 44.8% of the individuals with MCI revert to normal cognition at 2-year follow up [48, 54], suggesting considerable instability in the MCI diagnosis.

In the 90-plus population, only the 90+ Study had specifically examined the MCI using slightly modified MCI criteria [43]. Non-demented individuals were classified as normal, aMCI, naMCI and other cognitive impairment (OCP), the last defined as impairment in daily functioning, or in MMSE (< 24), or both. Prevalence of aMCI, naMCI, and OCP were found to be 8.1%, 8.1% and 18.0% respectively; and dementia incidence was found to be the highest in aMCI and OCP subgroups, being 31.4 and 39.9

per 100 person-years respectively compared to that in normal (8.4 per 100 person-year) and naMCI subjects (14.1 per 100 person-years) [43]. These findings are consistent with results in the younger elderly, yet more studies are obviously warranted to validate the findings in exceptional longevity.

1.3.3 Neuropathological substrate of MCI

In the general elderly population, the neuropathological substrate of MCI is found to be qualitatively similar to that of dementia, but of less severity in general [45, 55, 56], suggesting a transitional stage of evolving dementia. The aMCIs (single-domain and multidomain) were initially conceptualised as prodromal stages of AD [39]; and indeed, AD pathology is found to be the most common on autopsy examination [55, 57, 58]. However, other concomitant pathologies such as AGD, HS and vascular pathology are common in aMCI [55, 59]. Moderate to severe AD pathology had also been reported in 49.2% of the naMCI individuals, compared to 58.7% in aMCI subjects [58]. These findings indicate that both amnestic and non-amnestic subtypes are associated with an increased risk of AD dementia.

Further, in the 90-plus population, none of the established neuropathological makers (AD pathology, vascular pathology, HS and pathological 43-kDa transactive response sequence DNA-binding protein [TDP-43]) was found to distinguish normal cognition from cognitive impairment no dementia [60]. This indicates limitations of using single pathology in explaining early cognitive dysfunction at advanced ages.

Collectively, MCI could be regarded as a possible predementia phase of cognitive dysfunction, and has clinical implications in early diagnosis and possible interventions of dementia. However, there is a lack of substantial research into MCI in the oldest old, due to the conceptual ambiguity as well as difficulties in operational definition of

"cognitive impairment". The neuropathological basis of MCI in the oldest old remains poorly understood, and new markers are warranted to identify MCI or "milder level of cognitive impairment" before clinically overt dementia.

1.4 Structural MRI studies of brain ageing

High-resolution brain MRI has an advantage over neuropathology in that it is *in vivo* and non-invasive. Even in high-quality neuropathological studies, the median interval between last cognitive assessment and brain autopsy was long, varying between 7.5 and 19 months [27, 60-62], during which substantial cognitive decline could have occurred, in particular among the oldest old [63]. With structural MRI, the interval between clinical and imaging evaluation can be shortened to a few days. In addition, the assessment of brain vascular injuries, such as white matter hyperintensities (WMHs) [64] and brain infarcts [65], has been standardised and quantified on structural MRI, thus providing a better estimation compared to neuropathological assessment.

Neuroimaging studies of brain ageing and dementia are scarce in the oldest old. Only a few studies of post-mortem MRI (n=132, 85-plus) [66, 67], functional MRI (n=12, 90-plus) [68] and positron emission tomography (PET) amyloid imaging (n=13, 90-plus) [69] are currently available; yet none provide a comprehensive view of brain structures in exceptional longevity. The structural brain MRI profiles of normal and pathological ageing remain largely undetermined at advanced age.

1.4.1 Normal brain ageing in the young old

From 20-plus to 80-plus years, normal brain ageing has been extensively examined using structural brain MRI, yielding a non-linear and heterogeneous pattern of age-related brain loss [70]. Both longitudinal [71-73] and cross-sectional studies [74-76] have reported a turning point at approximately 65 years, after which the age-related

brain loss becomes more prominent compared to that in middle age. From 65 years and onward, accelerated brain loss has been reported in the hippocampus and entorhinal [73, 74, 77, 78], occipital [72] and orbitofrontal cortices [79] in some but not all [71], longitudinal studies. Findings from large cross-sectional samples also suggested greater volume loss of hippocampus in the older age range [75, 76]; yet linear negative relationship of age with brain structures was also widely reported [5]. Taking the brain as a whole, a "frontotemporal" pattern of age-related brain loss, from 65 to 90 years, is recognised by both longitudinal [72, 77, 79, 80] and cross-sectional [75, 76, 81] reports. That is, the frontal cortices and medial temporal lobe are noted as the brain regions most susceptible to the effects of age.

One popular view to explain the frontotemporal pattern was the "last in, first out" or "retrogenensis" hypothesis [82, 83], which postulated that the late-maturing, more complex brain areas (such as medial prefrontal cortex) are affected during early stages of ageing. However, this model is inconsistent with the prominent age-related decline of medial temporal lobe, which is considered to have less complexity compared to the prefrontal cortex [84, 85].

Another recent focus has been on the default mode network (DMN) as being a prime target of change in brain ageing. The DMN is comprised of a specific set of brain areas that are active when the individual is at wakeful rest [86]. Key structures of DMN (rostral middle frontal, orbitofrontal, middle temporal cortex, inferior parietal, precuneus and entorhinal cortices and hippocampus) had been found to overlap considerably with the brain areas that experience greatest age-related atrophy in normal ageing [80, 86]. However, the most age-sensitive (frontotemporal) brain areas include, but are not restricted to, the DMN hubs. Early amyloid deposition and disruption of the

connectivity has been reported within the DMN [87, 88], suggesting the vulnerability of DMN in AD, and not being specific to normal ageing.

Both hypotheses capture some, but not all, critical features of brain ageing in the young old; yet it is unknown if these theories would be upheld when applied to the healthy oldest old, a model of successful ageing.

1.4.2 Normal brain ageing in the oldest old

The structural MRI profile of normal brain ageing beyond 90 years remains under-explored. Even in large cross-sectional samples, the 90-plus group was often combined with octogenarians (age range 80 – 95 years, n=14 - 38) [76, 89], and the estimated age-related differences (-1.0% to -2.4% per decade for cerebral cortex) were found to be much smaller compared to the estimates within the age range 60- 79 years (-6.1% to -6.2% per decade) [76, 89]. Such results are inconsistent with previous longitudinal observations, which suggest linear or accelerated brain loss with increasing age [72]. The small sample size, limited MRI-derived measures, and potential sampling bias need to be taken into account. Larger and more representative samples are warranted to clarify this discrepancy.

Moreover, being 90-plus years and dementia-free may have a twofold impact on structural MRI profiles. First, these individuals are thought to be a group who "delayed" or "escaped" the process of dementia before the age of 90 years [17, 18]. In young old, the cognitively "non-decliners" are considered to have preserved volumes of certain brain structures, such as the prefrontal cortex and hippocampus [90, 91]; and this might also be the case in the oldest old. Second, absence of dementia does not indicate a lack of neuropathologies. Both vascular pathologies and varying neurodegenerations, such as

AD pathology and HS, increase substantially with advancing age [4]; and are likely to contribute to the neuroimaging features of the exceptionally old brains.

Consequently, structural MRI profiles of the 90-plus population may be distinct from those septuagenarians and octogenarians. The pattern and the magnitude of the brain ageing at advanced age on structural MRI warrant systemic investigations.

1.4.3 MRI Markers of cognitive impairment in the young old

Cerebral atrophy on structural MRI is the most common finding in the process of both ageing and dementias. However, the rates of dementia-associated cerebral atrophy are several times higher than in normal ageing [5]. In addition, distinct patterns of the grey matter loss could assist in differentiating between the underlying aetiologies of cognitive impairment, the most common in late life being AD pathology, LRP, brain vascular injuries and their varying combinations.

The structural MRI signature of the prodromal and clinical AD has been the most researched. Through serial structural MRI scans, the progression of cerebral atrophy in subjects with aMCI that convert to clinical probable AD is characterised by earliest changes in the medial temporal lobe, including the anterior part of hippocampus and entorhinal cortex [92-96], followed by involvement of the temporal and temporoparietal association cortices [92, 97-99], and eventually widespread neocortical atrophy [92, 100, 101]. These suggest that AD-associated brain atrophy follows a temporal-to-parietal gradient in its progression, which corresponds well with the Braak and Braak neurofibrillary pathological staging schema in AD [102]. It should be noted that although hippocampal atrophy is the most established MRI marker of dementia, in particular clinical AD [103], it is also thought to be a feature of HS and CAA, and thus is not specific to AD pathology [9, 104, 105].

Different from AD, cerebral atrophy of dementia with Lewy bodies (DLB) had been found to be more focused on midbrain, substantia innominata and parietal cortex, with a relative sparing of the medial temporal lobe [106, 107]. This pattern supports the proposed pathological development of Parkinson's disease and DLB [108], and could be used in distinguishing DLB from AD at a group level.

In subjects with MCI, regarded as a prodromal dementia, atrophy patterns on neuroimaging are associated with the cognitive deficit in specific domains. While prominent grey matter loss in the medial temporal lobe was invariably reported in amnestic MCIs [109-111]; more heterogeneous atrophy patterns were found in non-amnestic MCI subtypes, i.e., atrophy of the anterior temporal cortex being associated with language impairment, and atrophy of the basal forebrain and hypothalamus being associated with attention and executive deficits [112]. These patterns concord with the earlier discussed MRI signatures of different dementias; thus could provide insight into the possible aetiologies and the subsequent course of the disease.

Vascular lesions, most commonly white matter hyperintensities (WMHs) and brain infarcts, have also been associated with poorer cognition, subsequent cognitive decline and a higher risk of developing dementia [8, 113]. Vascular cognitive impairment (VCI), a spectrum of cognitive impairment of vascular origin, is found to vary from subtle cognitive disturbance to frank dementia, depending on the severity and location of vascular pathology [114]. Findings on structural MRI, such as extensive deep or confluent WMHs (rather than periventricular WMHs) [115], multiple infarcts [116], involvement of strategic locations (basal ganglia and thalamus) [117] and combined vascular injuries [118-120] have been associated with more severely impaired cognition in most studies, although a few studies have reported negative results [121, 122].

Symptomatic and silent brain infarcts have been found to have similar effects on cognition [113]. Although the brain vascular injuries have been reported to affect all cognitive domains [115, 116, 123], impairment in processing speed, working memory and executive function has been the most common [123-126].

Some earlier reports argued that the cognitive impairment associated with vascular lesions was mediated by global and frontal cortical atrophy [121, 127]; however, increasing evidence suggests vascular pathologies being at least partly independent processes that affect cognition [128-130]. Therefore, the extent and severity of brain vascular injuries on structural MRI should be examined in combination with cerebral atrophy, to determine the contribution of each of these markers to cognitive functioning.

1.4.4 MRI Markers of cognitive impairment in the oldest old

Only one study, the Vantaa 85+ Study in Finland, had examined the markers of cognitive impairment in the 85-plus group using post-mortem MRI. Clinical dementia was strongly associated with the medial temporal atrophy [66], but not with the presence of the WMHs [131]. These results concord with a few PET amyloid imaging studies in the elderly aged 82- 99 years, reporting a faster cognitive decline in non-demented individuals with greater β-amyloid deposition [69, 132]. Another study of a slightly younger population (mean age 85.5 years) showed that a combination of β-amyloid deposition, hippocampal atrophy and WMHs was associated with a high risk of dementia [133].

Collectively, these findings suggest that hippocampal atrophy and brain vascular injuries may serve as markers of prodromal and clinical dementia in the oldest old. However, several limitations are noteworthy in the previous investigations. First, only limited MRI-derived measures were included in analyses. It remains unclear whether

the atrophy of cortical regions of interest (ROIs), brain infarcts and quantitative WMHs are independently associated with MCI or dementia at this age. Second, the relationship between brain pathology and clinical dementia is thought to be weaker at older age [4], yet it is unknown whether neuroimaging makers have the same pattern. Third, the sample size of individuals aged 95-plus was small in the previous studies and previous findings would need to be replicated with larger samples to better understand the association between cognitive dysfunction and MRI-derived brain measures.

1.5 Aims of this thesis

The neuroimaging features of brain ageing and prodromal and clinical dementia are under-explored in the oldest old. Currently available, but very limited, data suggest that the oldest old may have distinct neuroimaging profiles compared to their younger counterparts. Therefore, the overarching aim of this thesis is to characterise the structural MRI features of normal and pathological brain ageing from the eighth to eleventh decades of life, with a special focus on the oldest old (individuals aged 85 years or over).

Specific aims

1. To examine the relationship of age with structural MRI-derived measures in a sample of non-demented community dwelling individuals aged from 71 to 103 years; and to delineate the MRI profiles of those aged 90-plus years in comparison with younger individuals.
2. To delineate MRI markers of dementia at 80 and 95 years respectively, with the use of atrophy indices and vascular markers; and to test whether the association between structural MRI and clinical dementia is independent of age.

3. To explore MRI markers that could distinguish aMCI or naMCI from normal in an elderly population aged 71 to 103 years; and to investigate MRI structures that best distinguish aMCI from CN in the young old and oldest old respectively.

1.6 Population sample and methodology issues

Data presented in Chapters 3, 4 and 5 were obtained from participants recruited for the Sydney Centenarian Study (SCS) and the Sydney Memory and Ageing Study (MAS).

1.6.1 The Sydney Centenarian Study (SCS)

Initiated in 2008, the SCS is a longitudinal, population-based study of the elderly aged 95 years or above, who were comprehensively assessed biannually and were invited to complete a brain MRI at baseline. The principle aim of the SCS is to examine brain health in exceptional longevity, i.e., to examine cognitive and MRI profiles of the exceptionally long-lived individuals (95-plus years), and to explore determinants of successful cognitive ageing. Detailed methodology of this study has been previously published [15].

Participants were primarily recruited from seven select districts in the eastern suburbs of the Sydney metropolitan area in New South Wales, Australia, using a multi-pronged approach to obtain a representative sample. At baseline, participant-based evaluation comprised neurocognitive, psychiatric and medical assessments, which were conducted using standard instruments in three 1-hour sessions. Informant-based assessments included qualitative reports and quantitative informant questionnaires on the participant's cognitive change over time and daily functioning. As of August 2013, the SCS had recruited 409 participants at baseline, including 57 who completed a brain MRI.

1.6.2 The Sydney Memory and Ageing Study (MAS)

The MAS is a longitudinal, prospective cohort study of non-demented community-dwelling elderly, aged 70 to 90 years at recruitment, details of which have been previously described [134]. The primary aim of the MAS is to examine the clinical characteristics, incidence and prevalence of cognitive impairment over time. The study was initiated in 2005, and subjects were randomly recruited through the electoral roll from the same geographical area as in the SCS. A total of 1037 non-demented subjects were recruited and assessed at baseline, with 234 MRIs being completed by the same scanner as in the SCS. Participants receive detailed follow-up assessments every two years and brief interval follow-up yearly. To maximise the sample size, those MAS participants who converted to dementia and/or who became aged over 90 years in MAS follow-up waves (n = 59) were also included in this thesis. No participant was included twice.

1.6.3 Classification of cognitive categories

Cognitive categorisation of dementia and MCI was determined by a panel of at least three experienced specialists comprising an old age psychiatrist, a neuropsychiatrist and a neuropsychologist, based on: 1) detailed description from trained research psychologists, including the participant's general appearance, attitude or behaviours, and comments related to performance on tests, especially in relation to factors such as sensory impairment, motor constraint or limited English language that might affect neuropsychological performance; 2) qualitative reports from the informants who had regular contact (≥1 hour per week) with participants, plus quantitative informant questionnaires including the short form of the Informant Questionnaire on Cognitive Decline in the Elderly (Short IQ CODE) [135] and the Bayer activities of daily living scale (BADLs) [136]; 3) neuropsychological battery encompassing cognitive domains

important for the diagnosis of dementia including premorbid intelligence, attention/processing speed, memory, language, visuospatial ability and executive function. A small population of SCS participants (N=22) only completed the Addenbrooke's Cognitive Examination – Revised (ACE-R) [137] and could not tolerate a more detailed assessment.

All participants diagnosed with dementia met the DSM-IV criteria (Chapters 3, 4 and 5), that is, the development of multiple cognitive deficits that include memory impairment and at least one other cognitive disturbance in attention/processing speed, language, visuospatial ability or executive function. These cognitive deficits should be sufficiently severe as to result in a decline from previous higher level of functioning and impairment in performance of daily activities.

MCI was diagnosed (Chapter 5) according to the International Consensus Criteria and was further categorised into aMCI and naMCI subtypes [40]. Single- and multiple-domain MCIs were pooled together.

Defining cognitively high functioning (Chapter 3) was based on individual's intact neuropsychological performance across all tested cognitive domains (within 1.5 standard deviations of normative values) and a preserved level of functioning on instrumental activities of daily living (IADLs) according to informant reports and standardised IADL scales.

While age-stratified normative data for those < 90 years are widely available; for the 90-plus individuals, normative data from the 90+ Study was employed for the Boston Naming Test (BNT), letter fluency, animal fluency and MMSE [24]; performance on the remainder of the tests was judged against the next oldest available normative values. In order to define cognitive categories in participants who only completed ACE-R, an

individual's performance was compared against the mean and standard deviation of the high-functioning oldest old (within the same 95+ age range) who had completed the full neuropsychological battery.

1.6.4 Neuroimaging data

All participants were scanned using a Philips 3 T Achieva Quasar Dual scanner (Philips Medical Systems, Best, The Netherlands) located at Neuroscience Research Australia (NeuRA), Sydney, New South Wales, Australia. The acquisition parameters for T1-weighted 3D images were: TR = 6.39 ms, TE = 2.9 ms, flip angle = 8°, matrix size = 256 × 256, FOV = 256 × 256 × 190, and slice thickness = 1 mm with no gap in between, yielding 1 × 1 × 1 mm3 isotropic voxels. T2-weighted fluid attenuated inversion recovery (FLAIR) images were acquired in coronal orientation with acquisition parameters as: TR = 10000 ms, TE = 110 ms, inversion time TI = 2800 ms; matrix size = 512 × 512; slice thickness = 3.5 mm with no gap between slices, yielding spatial resolution of 0.488 × 0.488 × 3.5 mm3 per voxel.

The estimation of cortical and subcortical structures were carried out by the FreeSurfer and FMRIB Software Library (FSL) neuroimaging tools respectively, both of which have been validated against histological measures [138] or manually traced brain volumetrics [139]. T1-weighted imaging was processed by FreeSurfer version 5.3.0 for cortical volume and thickness, white matter volume and estimated intracranial volume (eTIV). Scans were segmented to yield data for volumetric and ventricular ROIs, as previous described [140, 141]. The cortical surface was reconstructed and parcellated into 34 cortical ROIs based on the "Desikan-Killiany" cortical atlas using an automated approach [141, 142]. Subcortical grey matter nuclei were processed with FSL using the FMRIB's Integrated Registration and Segmentation Tool [143, 144], as the previous

analysis showed higher intra-class correlation between hippocampal volumes processed by FSL and manual tracing (0.67, 95% confidence interval [95%CI]: 0.54 – 0.77) compared to that between FreeSurfer and manually traced results (0.46, 95% CI: 0.28 – 0.62) in 85 individuals.

The accumulation of WMHs was examined using our in-house method, which has been described in detail in a previous publication [64]. Briefly, the WMHs were quantified and extracted by an algorithm implemented in Matlab based on the signal abnormalities on FLAIR images, and were then classified into periventricular and deep WMHs using a predefined rim 7.5 - 10 mm from the ventricles.

The above systematic process involved quality control and manual editing by the candidate who was trained in neuroanatomy and neuroimaging. Since the rate of processing errors would be higher in brains with more atrophy or brains with more WMHs, all the 90-plus brains (initial n = 89, final used n = 70) were visually inspected and manually edited even when there were only minor processing issues, to ensure the most accurate output.

In those < 90 years (initial n = 234, final used n = 207), three approaches were used to correct the errors in the data processing: 1) the participants were sorted by descending order of volume of total WMHs, and visual inspection and manual editing were performed in all the brain MRIs with WMHs ≥ 15 ml; 2) all brain scans with "outlier" values (beyond 1.96 standard deviation) of the lobar cortical thickness or subcortical volumes were examined, and the data processing manually corrected if errors were detected; 3) all neuroimaging outputs were visually inspected after the manual editing, and those that failed the quality inspection were removed from the final data set.

MRI-defined small brain infarcts were determined by the candidate who was blinded to clinical data, applying the in-house protocol for cerebral infarcts and Virchow-Robin spaces. Small brain infarcts on MRI were defined as fluid-filled cavities of between 3-20 mm in longest diameter on T1-weighted imaging, most commonly surrounded by a hyper-intensity rim on FLAIR. Forty-eight scans with ambiguous lesions were reviewed in consultation with a neuroradiologist (Dr L. Dawes). Intra-rater test-retest reliability was excellent (k = 0.905), by scoring 100 scans twice, blinded to the initial rating and 1 month apart. Lacunar infarcts, cortical and cerebellar infarcts were combined in the present study, since the preliminary analyses showed similar results regardless of the location of the brain infarcts.

1.7 Outline of this thesis

This thesis comprises four studies. The first is a review of dementia in the 90-plus population, and is followed by three data-based studies investigating the structural MRI profiles of normal and impaired brain ageing from eighth to eleventh decades of life. A slightly different cut-off age (85, 88 and 90 years), to maximise the statistical power in each of the studies, was used to define the oldest old across the studies, with the oldest old group being the focus of this thesis.

1.7.1 Chapter 2: Dementia in the oldest old

The epidemiology, pathogenesis, and risk and protective factors of dementia after the age of 90 years were reviewed. As of March 2013, relevant publications were identified using the PubMed database. Population-based studies were of particular interest; and the prevalence, incidence and survival time of dementia in the 90-plus were summarised. Common neuropathologies and clinicopathological correlates of dementia were

examined in both the young old and oldest old. Finally, novel cognitive markers, factors affecting dementia, and future directions were discussed.

More recent publications, including a few updates in neuropathology and neuroimaging markers of dementia and MCI in the oldest old, have been incorporated in the Introduction (Chapter 1).

1.7.2 Chapter 3: Age-associated differences on structural brain MRI in non-demented individuals from 71 to 103 years

This study examined the cross-sectional brain morphological differences from 71 to 103 years in non-demented individuals by high-resolution structural MRI. A total of 277 non-demented participants from the SCS and MAS comprised the sample, including a subsample of 160 cognitively high-functioning elderly. Age-related differences on MRI-derived brain measures (volumes of grey matter, white matter and WMHs, and cortical thickness) were examined by general linear models. Structural profiles of the 90-plus were delineated, in comparison with that of their younger counterparts.

1.7.3 Chapter 4: Association between structural brain MRI and dementia in the eighth to eleventh decades of life

In this study, the associations between structural MRI-derived measures and dementia were examined as a function of age. A combined sample aged 71 to 103 years from the SCS and MAS were included in this cross-sectional investigation. Odds ratio of dementia in relation to MRI measures of atrophy (cortical and subcortical) and vascular pathology (WMHs and brain infarcts) were modelled at 80 and 95 years respectively, using logistic regression. Moderating effects of age were examined by testing the significance of the interaction of age and the MRI measures in the model.

1.7.4 Chapter 5: Structural MRI biomarkers of mild cognitive impairment from young elders to centenarians

The hypothesis in this study was that MRI signatures of MCI would be different in the oldest old compared to the young old. Participants aged 71 to103 years from the SCS and MAS were classified as aMCI, naMCI or cognitively normal (CN). Atrophy indices on structural MRI and WMHs associated with MCI subtypes and the effects of age were examined by general linear models. Reduced logistic regressions were applied to determine MRI markers that best discriminate aMCI from CN in the young old (< 85 years) and those oldest old (≥ 85 years).

1.7.5 Chapter 6: General discussion and future directions

In this chapter, the main findings from the thesis are summarised with major contributions to knowledge in the field of brain ageing in the oldest old highlighted together with some recommendations for future research.

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CHAPTER 2: DEMENTIA IN THE OLDEST OLD

2.1 Aims of the literature review

The aims of this review were to:

1. Integrate population-based epidemiology studies with age-specific and sex-specific estimations of the prevalence, incidence and survival time of dementia in the 90-plus population;
2. Summarise the epidemiology of the most common neuropathologies from the 8th to 11th decades of life; and to review the clinicopathological correlates of dementia in the 90-plus population;
3. Review the novel cognitive markers at advanced age;
4. Review factors associated with dementia status in the very old, including genetic and cardiovascular risk factors, and potential behavioural protectors.

Relevant publications were identified by conducting a literature search as at March 2013, using the PubMed database. Studies based on population-based samples from 18 epidemiology centres and 6 neuropathology research teams were included for the data integration. Reports from convenience samples in both the young old and oldest old were included in the discussion.

2.2 Publication: *Nat Rev Neurol*. 2013; 9(7):382-393.

Please refer to the following 17 pages.

Dementia in the oldest old

Zixuan Yang, Melissa J. Slavin and Perminder S. Sachdev

People over the age of 90 years—the oldest old—are the fastest growing sector of the population. A substantial proportion of these individuals are affected by dementia, with major implications for the individual as well as society. Research on dementia in the oldest old is important for service planning, and the absence of dementia at this exceptional old age may serve as a model of successful ageing. This Review summarizes population-based epidemiological studies of dementia and its underlying neuropathology in nonagenarians and centenarians. The available data, although somewhat limited, show an age-specific and sex-specific profile of dementia status in very late life, resulting from a variety of neuropathologies that often co-occur. Extensive overlap in neuropathology between cognitively normal and cognitively impaired individuals is evident despite challenges to gathering data particular to this population. A complex picture is emerging of multiple pathogenetic mechanisms underlying dementia, and of the potential risk and protective factors for dementia that interact with genetics and lifestyle in normal and exceptional cognitive ageing.

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Introduction

People aged 90 years and over, who can be regarded as the oldest old, are the fastest growing sector of the population in many developed countries, including Australia, the USA, Japan and Europe.[1] In the USA, the number of individuals aged 90 years and over is predicted to increase from the current 2 million to more than 8 million, thereby comprising approximately 2% of the population by 2050.[2] In Australia currently, 7.6% of the 65-plus population is aged ≥90 years. This age group is projected to increase sixfold to 10.1% of the ageing population by 2061.[3,4] Worldwide, centenarians are expected to reach as many as 2.2 million by 2050, which is a 15-fold increase of the current centenarian population.[5]

Dementia affects a substantial proportion of individuals among the oldest old, with major implications for individuals as well as society. The high prevalence of dementia is, for researchers, both a challenge and an opportunity: research on dementia in this population is important for health-care planning, and the absence of dementia at this age may serve as a model of successful ageing. Our current understanding of cognitive disorders and their underlying neuropathology in this age group is limited. The number of studies carried out to date is small, methodologies have varied, and an agreed definition of dementia is lacking.

In this Review, we summarize the population-based epidemiological studies of dementia status and neuropathology in nonagenarians (individuals aged 90–99 years) and centenarians, together referred to as the oldest old. Relevant studies of cohorts of 85-plus years that provide information on advanced age are also discussed. We outline the methodological challenges particular to population studies of the oldest old, the underlying mechanisms of dementia, and the potential risk and protective factors. Furthermore, we discuss future directions that may help in understanding successful brain ageing.

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Competing interests
The authors declare no competing interests.

Epidemiology

The challenges to dementia studies in the oldest old, together with sources of bias, have been reviewed elsewhere,[6–14] and are summarized in Table 1. To minimize potential bias in this Review, we have included epidemiological studies of the prevalence and incidence of dementia in cohorts that are representative of the population of interest, and we only included studies with 50 or more participants. We did not differentiate dementias with different aetiologies due to the large proportion of individuals in this age group who have dementia with a mixed aetiology.[15]

Demographics in selected studies

Population-based studies have shown a consistently higher proportion of females than males in nonagenarian and centenarian samples (50.0–86.2%[16–28] and 59.0–90.0%,[9,29–37] respectively; Table 2 and Supplementary Table 1 online). Very few individuals over the age of 105 years have been included in the analyses to date. Participants in many studies tend to be well-educated, upper middle class and in good health, all of which could lead to an underestimation of the prevalence of dementia.

Prevalence of dementia

The prevalence of dementia in the oldest old is highly age-specific and sex-specific. Approximately one in four

individuals aged 90–91 years is affected by dementia,[16,19] and this rate increases to approximately 50% in older nonagenarians (Figure 1).[19–24] Dementia prevalence is higher still in centenarians, ranging from 42–76%, with a median prevalence of around 60% (Table 2). The majority of studies of nonagenarians have used criteria from the revised third edition[38] and fourth edition[39] of the Diagnostic and Statistical Manual of Mental Disorders, but three studies (the Leiden 85-plus Study,[16] the Danish 1905 Cohort Survey[17] and the Cambridge City over-75s Cohort Study[28]) were restricted to using cut-offs on Mini-Mental State Examination scores[40] to make a diagnosis of dementia. The criteria used to diagnose dementia in centenarians are even more diverse, although if two studies (the Swedish[29] and New England[34] studies) are excluded, the reported prevalence is in a narrow range of 52–63%. In both nonagenarians[18–22,27,28] and centenarians,[9,29–31,37] the prevalence of dementia in males is consistently lower than in females. Most of these studies noted that individuals without dementia in these age groups often had mild levels of cognitive impairment, although the diagnosis of mild cognitive impairment was not generally used in these studies. Normal cognitive function was judged to be present in about one in three nonagenarians[17,19,21,22,28] and one in four centenarians (Table 2).[9,29–36] Definitions of normal cognitive function at this age, however, have relied on different parameters, including neuropsychological test performance within a particular range; functional independence in activities of daily living; good social functioning; and a general lack of disability.

A question that has often been asked is whether or not dementia is inevitable if an individual lives long enough. It is not possible to definitively answer this question, as the true limit of longevity is not known. However, the oldest recorded person in the world, who died at the age of 122 years and 164 days, was assessed at the age of 118 years and 9 months and was reported to perform comparably to a similarly educated person in their 80s on tests of verbal memory and language fluency.[41] Furthermore, she showed no evidence of progressive cognitive decline.[41] Another individual was assessed at 112–113 years and an autopsy was performed following her death aged 115 years. Her cognitive performance was reported to be better than that of the average healthy adult aged 60–75 years, and her brain showed remarkably little pathology,[42] again suggesting that cognitively normal ageing is possible in supercentenarians (individuals aged 110 years and over).

Key points

- People over the age of 90 years (the oldest old) are the fastest growing sector of the population, with a substantial proportion developing dementia
- The prevalence of dementia is age-specific: rates increase from about 25–30% in those in their early 90s to about 50% in the late 90s and 60% in centenarians
- Prevalence of dementia is lower in men than in women, but the incidence at 90 years or over does not differ by sex, suggesting shorter survival time in men
- Multiple neuropathologies underlie dementia, including Alzheimer disease neuropathological change and vascular pathology, which often co-occur, as well as Lewy-related pathology, hippocampal sclerosis and cerebral amyloid angiopathy
- Diffuse neocortical neurofibrillary tangles and neocortical and hippocampal atrophy are the most consistent correlates of dementia in the oldest old
- Neuropathology is common in cognitively normal individuals aged over 90 years, and better markers are needed to distinguish dementia from normal cognitive ageing

Incidence of dementia

Only a handful of studies have provided incidence data on dementia in the oldest old (Figure 2). Studies with sufficient data suggested that incidence rates increase beyond the age of 90 years.[43–50] The 90+ Study, which had the largest sample size of the studies we have identified, indicated that the incidence of dementia doubled every 5 years, from 12.5% per year for individuals aged 90–94 years to 21.2% in individuals aged 95–99 years and 40.7% in centenarians.[43] This study showed similar incidence rates for dementia in men and women.[43]

Survival

It has been proposed that long-lived individuals tend to 'compress morbidity'; that is, chronic illness is postponed with increasing age, such that long-lived individuals have

Table 1 | Challenges in population-based studies of cognition in the oldest old

Subject recruitment	Cognitive assessment and dementia diagnosis	Neuropathology sampling and diagnosis	Statistical methods
Difficulties in recruiting a representative study cohort	General fragility of patients, high morbidity and large daily cognitive fluctuation	Different and often low autopsy rates	Large amounts of missing data, particularly at follow-up
Age validity, inclusivity in a study and sample size	Rapid cognitive decline, sampling frequency and training effect	Distinct spectrum of neuropathology compared to younger elderly	Sample weighting due to disproportional sample size
High mortality and low rates of follow-up	Heterogeneity in neuropsychological assessment, and frequent ceiling or floor effects	Changes in sensitivity and specificity of conventional neuropathological protocols	Selection of a comparison group
Decline or withdrawal due to overprotective family and/or friends	Low reliability of informants' and participants' self-rating	Interval between last cognitive assessment and brain autopsy	Reduced statistical power due to use of nested models
Cohort effect	Little normative data, effects from different diagnostic criteria, and difficulties in dementia subtype identification	Lack of standardized neuropathological protocol for vascular pathologies	Age-specific and sex-specific effects on cognitive measurements

Table 2 | Prevalence of dementia in representative studies of centenarians

Study	Total number of participants (% female)	Diagnostic criteria	Age range (mean years ± SD)	Prevalence of dementia (%)			Participants with normal cognition (%)
				Total	Female	Male	
Swedish Centenarian Study[29]	100 (82)	DSM-III-R	100	27 (42)*	30	16	34
Georgia Centenarian Study[9]	244 (84.8)	GDS >3	98–108 (100.60 ± 2.04)	52.3	54.5	41.9	22.5‡ (22.7 female; 20.9 male)
Northern Italy Centenarian Study[30]	92 (59)	DSM-IV	100–107 (101.8 ± 1.6)	61.9	69.6	50	20.6‡ (16.1 female; 30.6 male)
Tokyo Centenarian Study[31]	304 (78.6)	CDR >0.5	100–107 (101.1 ± 1.7)	61.9	67.4	41.5	24.3‡ (19.2 female; 43.1 male)
Heidelberg Centenarian Study[32]	90 (90)	MMSE§ <11 or GDS >3	100 (100.20 ± 0.41)	52 or 59‖	NA	NA	25
Danish Centenarian Study[33]	207 (78)	ICD-10	100	51	NA	NA	25
New England Centenarian Study[34]	74 (86)	CDR >0.5	100–110	76	NA	NA	16.2
Korean Centenarian Study[35]	89 (87.6)	CDR >0.5	100–115 (102.4 ± 2.6)	61.8	NA	NA	6.7
Finnish Centenarian Study[36]	179 (84.4)	DSM-III-R	100–NA	56	NA	NA	44
Sydney Centenarian Study[37]	200 (70.5)	MMSE <24	95–106 (97.40 ± 2.29)	54	51.4	44.1	NA

*Number in parentheses is the prevalence of dementia after inclusion of individuals with dementia who were withdrawn from the study. ‡Prevalence in total cohort. §Short version with full score at 21. ‖Prevalence based on MMSE and GDS cut-offs. Abbreviations: CDR, clinical dementia rating; DSM, Diagnostic and Statistical Manual of Mental Disorders; DSM-III-R, DSM-III, revised; GDS, global deterioration scale; ICD, International Statistical Classification of Diseases and Related Health Problems; MMSE, Mini-Mental State Examination; NA, not available.

relatively short periods of age-related morbidities.[51] Current data, although limited, suggest that a similar phenomenon applies to cognitive functioning. Evidence has shown that cognitive ability declines increasingly from late in the ninth decade to the 12th decade of life[32,52,53] across most cognitive domains, affecting both fluid and crystallized intelligence.[54] Despite this age-related decline in cognitive ability, dementia-free survival is thought to increase with advanced age. The onset of cognitive impairment is estimated to have a 3-year delay for each decade of life from 90 years onwards, followed by a rapid cognitive decline toward the end of life.[52]

Cognitive impairment is independently associated with mortality in the oldest old after adjusting for potential confounders, such as apolipoprotein E (*APOE*) genotype and various comorbidities.[17,55,56] In this population, longer survival time for those with dementia appears to be associated with female sex and younger age of dementia onset.[57–59] The median survival in individuals with dementia onset after 85 years was reported to be less than half that for individuals with onset 20 years earlier (2.76 years versus 5.70 years).[60] In another study, the median survival for patients with onset of dementia after 90 years was 1.46 years in men and 2.46 years in women.[17]

Neuropathology

The use of an autopsy cohort that is representative of the population is critical in evaluating the prevalence of neuropathological changes, clinicopathological correlations, potential risk factors and protective mechanisms in the oldest old.[13] We identified six population-based neuropathological studies (Table 3) that included more than 30 individuals aged 90 years or over: the Hisayama Study (Japan),[61,62] the Vantaa 85+ Study (Finland),[63–66] the Medical Research Council Cognitive Function and Ageing Study (MRC–CFAS) in the UK,[24,67,68] the Honolulu–Asia Aging Study (HAAS) in the USA,[69,70] the 90+ Study (USA)[2,71] and the Georgia Centenarian Study (USA).[72]

Several neuropathological correlates of dementia are recognized in elderly populations, including neocortical and hippocampal atrophy, neocortical neurofibrillary tangles (NFTs) and neuritic plaques, vascular pathology, Lewy-related pathology (LRP) and hippocampal sclerosis (Box 1).[15,73] NFT-predominant dementia (NFTPD)[74–76] and argyrophilic grain disease[77,78] have also been reported in nonagenarians and centenarians, but the prevalence of both pathologies in the 90-plus population has not been quantified in a representative cohort. Therefore, these two types of pathology, when combined with less common neuropathologies (for example, frontotemporal dementia or corticobasal degeneration), are beyond the scope of this Review. In the oldest old, a distinct spectrum of neuropathology from that observed in the younger elderly has been noted, characterized by differences in the burden of various neuropathologies and the common occurrence of multiple pathologies.

Common neuropathologies

Cerebral atrophy, a nonspecific marker of accumulated neural insults, becomes substantially more common from the eighth to the 11th decade of life (Table 3). In the MRC–CFAS , the prevalence of both hippocampal and neocortical atrophy was more than twofold greater in individuals aged 90–94 years and more than threefold greater in individuals aged over 95 years than in those under 80 years.[24] Similar results were reported from the HAAS.[69]

The prevalence of the most common neurodegenerative changes—Alzheimer disease (AD) neuropathological change and LRP—was found to stabilize after the age of 90 years, although a sharp increase in their prevalence has been observed from the eighth to ninth decades of life (Table 3). The prevalence of moderate to severe AD neuropathology in the oldest old, which modestly exceeded that in octogenarians, was reported at 58.2–77.0% for NFTs and 52.6–60.0% for neuritic plaques, with NFTs consistently more prevalent than neuritic plaques.[2,24] The 90+ Study reported that 54% of the oldest old met the diagnostic criteria for intermediate to high likelihood of AD,[2] as set out by the National Institute on Aging–Reagan Institute Working Group.[79] Another study involving a convenience sample of 179 patients suggested that the prevalence of diffuse neocortical NFTs with appreciable neuritic plaques decreased after the age of 95 years.[72] The steady but low rate (37.5%) of increase in prevalence of AD neuropathology beyond 90 years of age in Japanese-American men, as reported in the HAAS, may be attributable to the effects of strict criteria for AD pathology, exclusive male recruitment, and ethnicity.[69] When individuals aged 90 years and older were compared with octogenarians, both the presence of any LRP subtype[61] (in 30% of the 90-plus age group versus 33% of octogenarians) and a moderate to severe degree of LRP[63] (27–28% versus 35%) were slightly less widespread. The prevalence of cortical LRP in the oldest old was reported to be 18.5% and 8.0% in the HAAS and the 90+ Study, respectively.[2,69] No association was found between sex and the prevalence of LRP,[61,67] although controversy exists regarding selective vulnerability to neuropathology in males[63] and a more diffuse anatomical distribution of lesions in females.[80]

Vascular pathology is heterogeneous: cerebral small vessel disease and related vascular brain lesions generally seem to increase in prevalence with age, although estimates vary widely between studies. According to the MRC–CFAS, small vessel disease affects approximately two-thirds of individuals in their 70s, rising to around three-quarters of the oldest old.[24] In the HAAS, the prevalence of microinfarcts was stable across all ages—that is, present in around one-third of individuals.[69] In addition to these population-based data, studies with large convenience samples (n >1,000) indicated a more marked increase in vascular pathology in very late life.[81,82] Valid comparisons are difficult, however, as these studies used different methods to assess pathology.

Cerebral amyloid angiopathy (CAA) and hippocampal sclerosis were found to be more common in the oldest old than in the younger elderly.[62,65,68] The prevalence of CAA was shown to almost double from the eighth to the 10th decade of life in the Hisayama Study[62] and the MRC–CFAS.[68] Data from the Vantaa 85+ Study indicated a high prevalence of CAA regardless of age—reaching 69.6% of the 306 patients aged 85 years or older—with greater frequency and severity in males.[65] Different rating methods and protocols to assess pathology may account for the discrepancy between these studies. The rising severity of CAA with advancing age also needs to be highlighted.[83] Hippocampal sclerosis becomes increasingly prevalent beyond the age of 90 years, reaching 11.0% in nonagenarians[2,69] and 17.6% in centenarians.[72] In a recent study with by far the largest series of pathologically confirmed cases to date of hippocampal sclerosis (convenience sample, mean age 91–92 years), it was reported to be associated with aberrant TAR DNA-binding protein 43 (TDP-43) expression in nearly 90% of patients with this pathology, compared with less than 10% of hippocampal sclerosis-negative individuals.[72] Moreover, hippocampal sclerosis in those aged more than 90 years occurred independently of cerebral infarcts or LRP, yet was slightly over-represented in cases with AD neuropathology.[72] The overall neuropathological profile suggested that hippocampal sclerosis—often associated with TDP-43—in the oldest old might be a distinct pathological entity associated with advanced ageing that

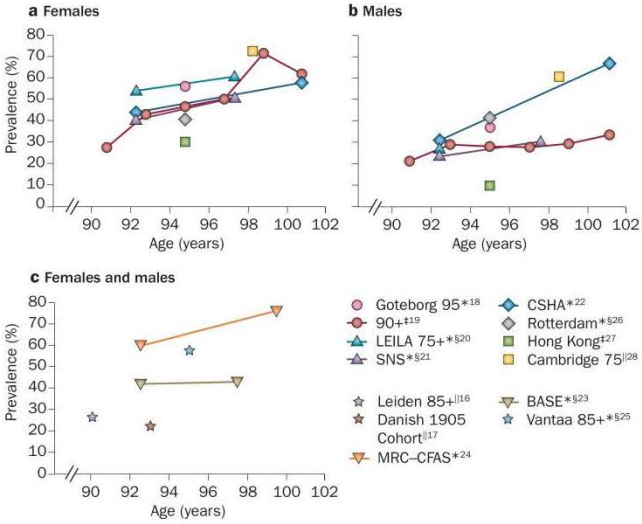

Figure 1 | Prevalence of all-cause dementia in population-based studies of individuals aged ≥90 years. Values on the x-axis are mean ages (or median age for 100-plus group in the 90+ Study[19]). Each line represents a single study. Prevalence of dementia increases rapidly with age in the oldest old, with a lower rate in men than in women. *Diagnosis using DSM-III, revised.[38] ‡Diagnosis using DSM-IV.[39] §Age 99 years has been applied to studies in which no upper age limit was indicated. ‖Diagnosis using Mini-Mental State Examination[40] cut-offs <22/30, <19/30 and <18/30 in the CC75C study,[28] Leiden 85-plus Study[16] and Danish 1905 Cohort Survey,[17] respectively. Abbreviations: BASE, Berlin Aging Study; CC75C, Cambridge City over-75s Cohort Study; CSHA, Canadian Study of Health and Aging; DSM, Diagnostic and Statistical Manual of Mental Disorders; LEILA75+, Leipzig Longitudinal Study of the Aged; MRC–CFAS, Medical Research Council Cognitive Function and Ageing Study; SNS: Stockholm Nonagenarian Study.

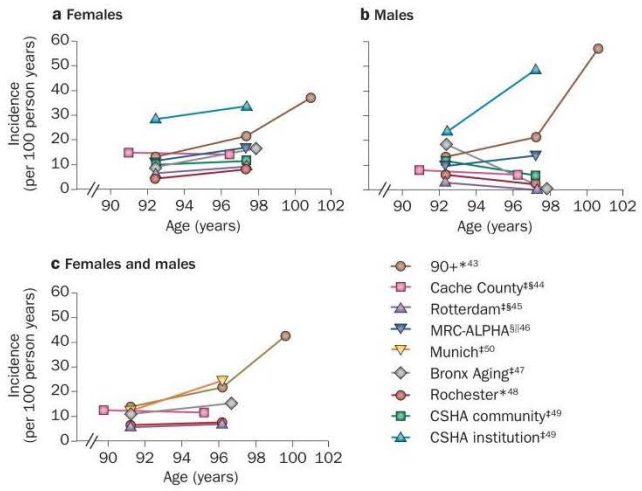

Figure 2 | Incidence of all-cause dementia in population-based studies of individuals aged ≥90 years. Values on the x-axis are mean ages (or median age for 100-plus group in the 90+ Study[43]). Each line represents a single study. Incidence of dementia continues to increase beyond the age of 90 years without obvious differences according to sex. *Diagnosis using DSM-IV.[39] ‡Diagnosis using DSM-III, revised.[38] §Age 99 years has been applied to studies in which no upper age limit was indicated. ‖Diagnosis using the 10th revision of the International Statistical Classification of Diseases and Related Health Problems.[148] Abbreviations: CSHA, Canadian Study of Health and Aging; DSM, Diagnostic and Statistical Manual of Mental Disorders; MRC-ALPHA, Medical Research Council Ageing in Liverpool–Health Aspects.

is different from other known subtypes of hippocampus sclerosis in the younger population.

The above pathologies, although common on their own, often co-occur in the oldest old. The extensive overlap of AD and vascular pathology was reported in three of the above studies (the MRC–CFAS,[84] the HAAS[69] and the 90+ Study[2]) and in a volunteer cohort.[85] This observation was supported by a study of a large sample of hospital patients ($n = 1{,}700$), which found that combined AD and vascular pathologies showed the most substantial increase in prevalence between the 60-plus and 90-plus age groups.[86] In addition, the coexistence of various neurodegenerative processes, particularly the combination of AD neuropathology with LRP[63,80] or CAA,[83,87] has been well-documented in the general elderly population, but the prevalence of these combined pathologies in the oldest old is still unclear.

Clinicopathological correlates of dementia

The clinicopathological correlates of dementia in the oldest old are not completely understood. The relationship between AD pathology and dementia has been the most studied, whereas correlations between other neuropathologies and cognitive disorders are underexplored (Table 4).

Neurofibrillary tangles and Lewy bodies

Diffuse neocortical NFTs (Braak stages[88] V and VI) are strongly indicative of dementia across all ages,[24,68,69,71] whereas neuritic plaques and moderate spread of NFTs (Braak stages[88] III and IV) are less reliable indicators owing to an overlap in their occurrence in the oldest old with and without dementia.[24,89] The relationship between AD neuropathology and clinical dementia is somewhat tenuous in the oldest old, for several reasons.

First, the distribution of pathology seems to be distinctive in the oldest old, which makes it difficult to apply the Consortium to Establish a Registry for Alzheimer's disease (CERAD) protocol[90] or Braak staging.[88] The density of AD neuropathology, in particular NFTs, is increased in the cognitively normal oldest old,[91] whereas individuals with 'pure' AD tend to have less-severe AD neuropathology than those of a younger age.[91,92] Data from another convenience sample suggest that NFTs are more likely to be concentrated in the hippocampal region—a subtype of AD known as limbic-predominant—in older patients with AD (mean age 86 years) than is typical for patients with AD in general (mean age 79 years).[93]

Second, compensatory mechanisms of cognitive functioning in the presence of pathology might be different in the oldest old. The fact that neocortical NFTs are more indicative of dementia than are neuritic plaques at this age implies that the aged brain could more readily compensate for the latter than the former.[94] It has also been suggested that a new and more sophisticated rating scale must be developed for neuritic plaques.[71]

Last, the effects of other factors on the pathogenesis of dementia should not be underestimated.[14] In a selective cohort with 'pure' AD neuropathology, the correlation between pathological burden and cognitive function was found to be consistent from the seventh to 10th decades of life, which was not the case when various combined pathologies were present.[95] Another study showed that among the oldest old, individuals with mixed AD and infarct pathology were more likely to present with dementia than were those with AD neuropathology alone.[85] Moreover, after adjustment for the presence of infarcts and LRP, the relationship between a pathological diagnosis of AD and dementia was significantly weaker than in the younger old (65–89 years), implying contributions from additional factors.[85]

Given the weakening of the relationship between neuropathology and dementia with age, the capacity of the oldest old to remain cognitively intact in the face of considerable neuropathology deserves attention. In contrast to the younger population,[96–98] longitudinal data in the 90+ Study showed that the cognitive trajectory in long-lived individuals without dementia was very similar in the presence and the absence of AD neuropathology.[99] This finding suggests that some of the oldest old might be more capable of tolerating neuropathology and, hence, maintaining cognitive function. More studies on this topic are warranted.

Diffuse neocortical LRP has also been found to be indicative of dementia (an association that seems to be independent of age),[2,63,69,85] but to a lesser extent than AD neuropathology. The relationship between other LRP subtypes and cognitive impairment is inconclusive.[63,71]

Table 3 | Epidemiology of neuropathology in individuals from the eighth to 11th decades of life

Study	Age range at death (years)	Prevalence of neuropathology (% of patients)								
		Hippocampal atrophy	Neocortical atrophy	NFTs*	NPs*	Small vessel disease‡	Multiple vascular pathology	LRP§	HS	CAA‖
MRC–CFAS[24,67,68]	<80	15.8	15.0	33.2	31.7	64.5	29.3	15.6	NA	14.3
	80–84	23.5	30.1	62.7	49.3	63.1	29.3	(total	NA	18.9 (80–89 years)
	85–89	33.7	41.3	55.2	48.3	70.0	43.0	cohort)	NA	
	90–94	32.2	39.8	58.2	54.1	76.3	36.7		NA	24.6 (90+ years)
	>94	50.0	58.5	61.4	52.6	76.4	38.9		NA	
HAAS[69,70]	72–79	NA	27.5	13¶	13¶	30.5	NA	4.0	1.0	44.1 (total cohort)
	80–84	NA	31.5	15.5¶	15.5¶	31.5	NA	16.0	11.0	
	85–90	NA	43.0	28.0¶	28.0¶	33.0	NA	12.5	12.0	
	90+	NA	64.5	37.5¶	37.5¶	32.5	NA	18.5	11.0	
Vantaa 85+ Study[63–65]	85–89	33.3 (total cohort)#	NA	70.4 (total cohort)	NA	NA	NA	35.0	NA	62
	90–94		NA		NA	NA	NA	27.0	NA	72
	95+		NA		NA	NA	NA	28.0	NA	70**
The 90+ Study[2,71]	92–106	NA	NA	77	60	12.4	30	8	11‡‡	52
Hisayama Study[61,62]	70–79	NA	NA	NA	NA	NA	NA	15.0	NA	20.6
	80–89	NA	NA	NA	NA	NA	NA	33.0	NA	36.9
	90–99	NA	NA	NA	NA	NA	NA	30.0	NA	45.2
Georgia Centenarian Study[72]	102.2§§	NA	NA	NA	NA	NA	NA	NA	17.6	NA

*Braak neuropathological stages[88] III–VI for NFTs and moderate to frequent neocortical NPs as described in the Consortium to Establish a Registry for Alzheimer's Disease protocol[90] unless otherwise indicated. ‡Different pathological protocols were used across studies: presence of any small vessel disease (severe arteriosclerosis, lacunes, microinfarcts or severe white matter attenuation) in MRC–CFAS;[24] presence of microinfarcts in 90+ Study;[2] and ≥2 microinfarcts found on review of eight haemotoxylin and eosin stained samples from neocortex or ≥2 microinfarcts on review of six sections of left and right side stained samples from the caudate, putamen and thalamus or ≥2 subcortical microvascular infarct units in HAAS.[69] §Different pathological protocols have been used across studies: moderate to severe LRP including limbic and diffuse neocortical subtypes in MRC–CFAS[67] and Vanta 85+ Study;[63] presence of Lewy bodies in Hisayama Study;[61] presence of cortical LRP in HAAS[69] or diffuse neocortical LRP in the 90+ Study.[2] ‖Different pathological protocols have been used across studies: Severe CAA in MRC–CFAS;[68] mild to moderate CAA in the 90+ Study;[71] presence of CAA in the HAAS,[70] Vantaa 85+ Study[65] and Hisayama Study.[62] ¶Alzheimer disease neuropathology classed as Braak stage ≥IV and ≥0.2 NP per mm2 and NFTs ≥2 per mm2.[69] #Medial temporal lobe atrophy scores>2 at postmortem MRI.[64] **Prevalence in participants aged 95–99 years whereas prevalence was 75% in participants aged 100–106 years.[65] ‡‡Prevalence reported as 17.6% (19 of 108) in another paper on the same study.[71] §§Mean age. Abbreviations: CAA, cerebral amyloid angiopathy; HAAS, Honolulu–Asia Aging study; HS, hippocampal sclerosis; LRP, Lewy-related pathology; MRC–CFAS, Medical Research Council Cognitive Function and Ageing Study; NA, not available; NFTs, neurofibrillary tangles; NPs, neuritic plaques.

Vascular pathology

Vascular pathology is another concern related to cognition. In the elderly, not only are small vessel disease,[100] infarcts (macroscopic[101] or microscopic[102]) and white matter lesions[103] associated with cognitive decline, but their presence may also lower the threshold of other pathologies to produce dementia. The effects of vascular pathologies on cognition in the oldest old remain unclear. Although the MRC–CFAS indicated that none of these heterogeneous pathologies were markers of dementia in the oldest old,[24] the negative impact of infarcts (in particular, microinfarcts) and/or atherosclerosis on cognitive function has been highlighted in a few studies of community-based and hospital-based cohorts.[85,104,105] The association between vascular pathology and dementia might be less pronounced in the oldest old, although certain pathological subtypes (for example, microinfarcts[102]) may make a more substantial contribution than others (for example, white matter lesions[106]) to dementia.

Cerebral amyloid angiopathy

The role of CAA in dementia is complex, as it includes elements of amyloid-associated pathogenesis and small vessel pathology. Moderate to severe CAA seems to be an independent discriminator of dementia across all age sectors, including the oldest old,[66,68] but the results of analysis of CAA regardless of severity are somewhat inconclusive.[83] Moreover, an additive effect of CAA and AD neuropathology on cognition in the elderly has been reported,[70] and there is an association between severe CAA, microinfarcts, and cerebral hypoperfusion;[107] these findings should be taken into consideration when undertaking studies of dementia in the oldest old.

Hippocampal sclerosis

An association between hippocampal sclerosis—often with TDP-43 pathology—and cognitive impairment has been observed in the oldest old.[2,72] Despite the overlapping clinical features of hippocampal sclerosis and AD, hippocampal sclerosis in advanced age (mean age 91–92 years) could be systematically differentiated from AD by a rapid decline in measures of hippocampal function such as delayed recall, and a better performance on neocortical tasks, such as verbal fluency.[72] Moreover, the clinical picture of age-associated hippocampal sclerosis does not resemble that of the other brain diseases associated with TDP-43 pathology, such as frontotemporal dementia in the younger elderly.[72]

Coexisting neuropathologies

In view of the distinct patterns of dementia-related neuropathologies in the oldest old, dementia status is less likely to be associated with one dominant neuropathology (for example, AD neuropathology or vascular pathology) than with their various combinations. Although the proportional contribution of

Box 1 | Common neuropathologies in the elderly population

Alzheimer disease
Alzheimer disease (AD) neuropathological change consists of neurofibrillary tangles and senile plaques. Neurofibrillary tangles are intraneuronal fibrils of hyperphosphorylated tau protein, typically located in limbic regions in early AD and progressing to widespread involvement of the neocortex in the later stages of the disease. Senile plaques consist of extracellular deposits of amyloid-β (Aβ) and have many forms, with neuritic plaques, defined as Aβ deposits in the centre of a cluster of dystrophic neurites, being most closely linked to neuronal injury.[108]

Lewy-related pathology
Lewy-related pathology (LRP) consists of neuronal Lewy bodies and Lewy neurites with abnormal aggregates of α-synuclein, which cause idiopathic Parkinson disease and dementia with Lewy bodies.[151] LRP affects selected neuronal populations and can be divided into three main subtypes with increasing severity: brainstem-predominant, limbic, and diffuse neocortical. Many instances of amygdala-predominant LRP have also been observed in pathologically confirmed AD.[152]

Vascular pathology
Vascular pathology includes infarcts, haemorrhages and diffuse white matter injury, and is another important cause of cognitive dysfunction known as vascular cognitive impairment (VCI). Cerebral microinfarcts that are composed of minute foci with neuronal loss, gliosis, pallor or cystic lesions have been recognized as important contributors to VCI.[153]

Cerebral amyloid angiopathy
Cerebral amyloid angiopathy (CAA) is characterized by the deposition of Aβ in cortical and leptomeningeal blood vessels (mainly the media and adventitial layers of small to medium vessels).[83]

Hippocampal sclerosis
Hippocampal sclerosis consists of cell loss and gliosis in the CA1 layer and subiculum of the hippocampus that is not related to AD neuropathology. Hippocampal sclerosis has been associated with various brain diseases, including pathological ageing in advanced age, epilepsy, tauopathy, non-tauopathy frontotemporal dementia, and cerebrovascular disease.[72]

each neuropathology to dementia might be different in the oldest old compared with younger age groups, atrophy, both of the hippocampus[24,64] and neocortex,[24,69] remains the most consistent correlate of dementia status across all age sectors. These observations suggest that standardized assessment of AD neuropathological change should be combined with assessment for other conditions that frequently co-occur,[108,109] and an algorithm that calculates the neuropathological burden—for example, the pathological index used in the HAAS protocol[69]—might be a consistent indicator of dementia in both the younger old and the oldest old. Moreover, additional factors may be determinants of cognition at very advanced age: these could include loss of neurons, axodendritic pruning and decreasing synaptic density, which are considered to be ageing-related[110] and may be reflected in a decrease in brain volume but not in conventional neuropathologies. Further systematic study, taking into consideration common coexisting neuropathologies and their potential interactive effects on cognition, is warranted. The complex interplay between increasing brain insults and decreasing cognitive reserve must also be considered in understanding the pathogenesis of dementia in the oldest old.

Novel cognitive markers

Conventional neuropathological markers mainly consist of insoluble protein aggregates and the resulting cerebral lesions that may cause neuronal dysfunction; however, they do not directly reflect neuronal function or neural circuit connectivity that contributes to cognition. When considering various neuropathologies versus potential compensatory mechanisms in the oldest old, markers that are related to neuronal activity might help to differentiate cognitive states. Distinct patterns of change in neuronal morphology as well as neuronal density have been observed in individuals who are ageing normally[111] and those who are ageing with AD neuropathology[112] (mean age 87–88 years). Moreover, although synapse loss has been argued as an important correlate of AD dementia,[113] a high level of presynaptic protein was reported as a component of cognitive reserve, protecting against various neuropathological burdens in very old age (88 years or older).[114,115] More research is necessary to verify these findings, especially in a representative population.

Table 4 | Clinicopathological correlates of dementia in the oldest old

Study	Atrophy		NFTs*		NPs‡		HS	LRP§	CAA	Vascular pathology
	Hippocampal	Neocortical	Moderate	Severe	Moderate	Severe				
MRC–CFAS[24,68]	++	++	+	++	–‖	–‖	NA	NA	+¶	–
90+ Study[2,71]	NA	NA#	–	+	–	+/–**	+‡‡	+	–	–
Vantaa 85+ Study[63,64,66]	+¶	NA	–	+¶	NA	NA	NA	+¶	+	NA
Honolulu–Asia Aging study[69,70,149]	NA	+¶§§	NA	+¶§§	NA	+¶§§	+¶§§	+¶§§	–¶‖‖	+¶§§
Georgia Centenarian Study[72]	NA	NA	NA	NA	NA	NA	+	NA	NA	NA

*Moderate and severe refer to Braak neuropathological stage[88] III or IV and stage V or VI, respectively unless otherwise indicated. ‡Moderate and severe indicate moderate and frequent neocortical plaque density according to the Consortium to Establish a Registry for Alzheimer's Disease protocol[90] unless otherwise indicated. §Diffuse neocortical subtype of LRP according to the revised consensus guidelines by the Third Consortium of Dementia with Lewy Bodies.[150] ‖Moderate to severe NPs in entorhinal cortex significantly correlated with dementia. ¶Significant CPC with dementia after adjusting for age (no separate group of 90+ years). #Significant difference in brain weight between participants with and without dementia. **Significant CPC with dementia only when measured by quantitative analysis of occupied area of NPs. ‡‡Significant correlation between limbic or neocortical TAR DNA-binding protein 43 immunoreactivity and dementia. §§Alternative neuropathological lesion indices used to specify neocortical atrophy, severe NFTs and NPs, hippocampal sclerosis, LRP and vascular pathology.[69] ‖‖CAA is a significant mediator of Alzheimer disease neuropathology and dementia, but is not an independent predictor of dementia. Abbreviations: +, significant CPC with dementia; ++, significant CPC with dementia as in younger elderly; +/–, inconsistent correlation or marginally significant CPC with dementia; –, no significant CPC with dementia; CAA, cerebral amyloid angiopathy; CPC, clinicopathological correlation; HS, hippocampal sclerosis; LRP, Lewy-related pathology; MRC–CFAS, Medical Research Council Cognitive Function and Ageing Study; NA, not available; NFTs, neurofibrillary tangles; NPs, neuritic plaques.

Neuroimaging studies of the oldest old are scarce—apart from several ongoing projects,[9,37,116] only a few studies involving postmortem MRI studies,[64,117] functional MRI[118] and amyloid imaging[119] are available. Preliminary results have suggested a negative effect of amyloid burden on cognition in the nondemented oldest old[119] and reduced brain activation in cognitively healthy nonagenarians.[118] Although there are practical limitations to carrying out such studies on frail elderly individuals, antemortem neuroimaging in particular would be of great value in understanding the temporal sequence and magnitude of a variety of pathological processes in relation to cognitive performance, as well as brain activation patterns in both cognitively impaired and high-functioning oldest old individuals.

Factors affecting dementia status

Cognitive status in the oldest old reflects a wide range of complex phenotypes resulting from both genetic and environmental factors. Although one might expect that a genetic contribution to exceptional longevity would be greatest at the oldest ages,[120,121] the extent to which cognition is influenced by genetic factors beyond the age of 90 years is largely unknown.[122] A wide range of genetic variants in the form of single-nucleotide polymorphisms (SNPs) have been found to be involved in determining lifespan, as well as cognitive status.[123–125] The *TOMM40–APOE* (translocase of outer mitochondrial membrane 40–*APOE*) region of the genome, which contains multiple SNPs, is the most important locus associated with both exceptional longevity and cognition.[120] In samples from younger old individuals (55–90 years), 10 other genes have been identified through large genome-wide association studies of late-onset AD,[124] and the *DCHS2* gene together with the *TOMM40–APOE* region has been significantly associated with age at onset of AD.[126] Of the genes mentioned above, only *APOE* has been systematically analysed in the oldest old.

Data on the cognitive effects of *APOE* alleles in the oldest old are mixed. From an epidemiological perspective, most population studies report not only a decrease in the frequency of the *APOE*ε4* allele, but also a reduced effect of this allele on the risk of dementia or mortality beyond the age of 90 years.[36,127–130] Neuropathological investigations, on the other hand, using the same cohorts as epidemiological studies (the 90+ Study and Vantaa 85+), have found a close association between the *APOE*ε4* allele and the full range of AD neuropathology,[25,131] as well as CAA,[66,132] in the oldest old. The *APOE*ε2* allele, surprisingly, seems to be associated with AD neuropathology, but not with dementia at this age.[131] Current discrepancies between clinical and neuropathological findings might be partly explained by the reduced clinicopathological correlations that we have discussed in this Review. Importantly, *APOE* affects neuropathology through multiple pathways,[133] and the role of its three isoforms, and their complex interplay with other genetic factors, in the determination of cognitive status is largely unknown.

A variety of risk factors for cardiovascular disease also seem to have different effects on cognition in the oldest old compared with younger individuals. The correlation between various vascular conditions and mild cognitive impairment is less obvious with increasing age.[134,135] Hypertension (systolic blood pressure ≥160 mmHg) in particular is strongly related to an increased risk of dementia in those aged 70–75 years.[136] In longitudinal studies of individuals over 85 years of age, however, high systolic blood pressure was not found to be harmful,[137,138] and even conferred protection against dementia,[139] whereas low diastolic blood pressure (≤70 mmHg) and reductions in blood pressure overall were associated with cognitive decline across a broad age range (70–95 years at baseline).[136,138,140] A protective effect against dementia—as yet inconclusive—has also been reported for hypercholesterolaemia in the eighth and ninth decades of life in prospective studies.[141,142] The timing of the emergence of risk factors for cardiovascular disease, as well as their duration, might be key determinants of their effects on cognition. The limits that define normality in cardiovascular conditions in advanced age need to be clarified to enable appropriate public health decisions to be made. In addition, longitudinal studies may help to identify the specific cardiovascular risk factors that influence cognitive decline in the oldest old.

Although numerous factors have been associated with differences in the prevalence of dementia,[9,17,31,143] few have been identified as risk factors for dementia in the oldest old. The only factors that predicted future development of dementia were advanced age and mild impairment in cognition (the amnestic subtype in particular) or function, such as in performing instrumental activities of daily living, indicating a pre-dementia status.[144] Education was not a significant protective factor;[144] however, mental stimulation[145] and a high level of leisure activities[146] in late life have been shown to be protective against cognitive decline in individuals aged 85 years or over, which supports the cognitive reserve hypothesis.[147]

Conclusions

Studies of cognitive impairment in the oldest old suggest an age-specific and sex-specific profile for dementia, with an overall pattern of accelerating cognitive decline and rapidly increasing dementia prevalence after the age of 90 years. Men, although under-represented in this sector of the population, seem to have a lower prevalence of dementia than women. The incidence of dementia may not in fact be different in the two sexes, however, as men with dementia could have a shorter survival time than their female counterparts.

The neuropathological basis of dementia is complex, with the coexistence of multiple pathologies being the most common determinant. In the oldest old, cerebral atrophy and diffuse NFTs remain strong indicators of dementia status despite a reduced clinicopathological correlation of dementia with AD neuropathology. The relative contributions from vascular pathology, hippocampal sclerosis, CAA and LRP to dementia need to be evaluated. A standardized neuropathological protocol

to assess heterogeneous vascular pathologies, including CAA, would be a major step toward understanding the attributable risk of having dementia in advanced age. New markers of pathology are also needed to differentiate dementia from normal ageing. Neuroimaging studies would be of substantial benefit in understanding the pathomechanisms of dementia, as well as patterns of functional compensation in the oldest old.

Cognitive status in the oldest old is the result of a lifetime's interaction between a variety of neuropathological insults and compensatory mechanisms involving genetic and environmental factors. High-functioning individuals, with or without ongoing neuropathological processes, might be considered as having aged successfully. Genetic and other determinants of cognitive impairment in this particular population need to be explored to uncover the mechanisms that determine the preservation of normal cognition well into exceptional old age. A consensus on the assessment and diagnosis of cognitive impairment in this age group will assist this process. Furthermore, an understanding of modifiable risk or protective factors is needed to inform preventative strategies at a population level.

Review criteria

References for this Review were selected by searching PubMed using combinations of the following terms: "ag*ing", "aged, 80 and over", "oldest old", "dementia", "cognition", "pathology", "Alzheimer's disease", "neurofibrillary tangles", "dementia, vascular", "cerebr*vascular disease", "Lewy body disease", "hippocampal sclerosis", "cerebral amyloid angiopathy", "epidemiology", "risk factors" and "mortality". We selected studies of dementia that met the following criteria: English language publications from 1992–2012; representative cohorts reporting epidemiology, neuropathology and neuroimaging findings for individuals aged ≥90 years; and detailed cognitive and/or neuropathological assessments and diagnostic criteria. Studies with a convenience sample of the oldest old and their younger counterparts were included in the discussion.

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Author contributions
Z. Yang researched the data for the article and wrote the manuscript. All three authors provided substantial contributions to the discussion of the content and to review and/or editing of the manuscript before submission.

Supplementary information is linked to the online version of the paper at www.nature.com/nrneurol.

Supplementary Table 2.1. Characteristics of population-based prevalence and incidence studies.

Study	Sample size (% female)	Age range (years)	Diagnostic criteria	Prevalence study	Incidence study	Follow up (years)	Interval (months)
Leiden 85+ Study [1]	274	90	MMSE <19	Yes	No	NA	NA
Danish 1905 Cohort [2]	1794 (72.6)	93	MMSE <18	Yes	No	NA	NA
Goteborg 95 Study [3]	338 (77.8)	95	DSM-III-R	Yes	No	NA	NA
90+ Study [4,5]	911 (77)	90 – 106/103*	DSM-IV	Yes	Yes	2.3 ± 1.3‖	6
LEILA 75+ [6]	119 (80.7)	90 – NA	DSM-III-R	Yes	No	NA	NA
SNS [7]	502 (83.1)	90 – NA	DSM-III-R	Yes	No	NA	NA
CSHA [8,9]	515 (78.3)‡	90 - 106/99*	DSM-III-R	Yes	Yes	5	NA
BASE [10]	52 (50)	90 – NA	DSM-III-R	Yes	No	NA	NA
MRC–CFAS [11]	163 (70.6)	90 – 103	DSM-III-R	Yes	No	NA	NA
Vantaa 85+ [12]	105/257§	90 – NA	DSM-III-R	Yes	No	NA	NA
Rotterdam Study [13,14]	266 (86.2)‡	90 – NA	DSM-III-R	Yes	Yes	5.7¶	36–48¶
Hong Kong Study [15]	140	90 – 99	DSM-IV	Yes	No	NA	NA
CC75CS [16]	161 (78.9)	90 – 106	MMSE <22	Yes	No	NA	NA
Cache County Study [17]	156	90 – NA	DSM-III-R	No	Yes	3#	36
MRC-ALPHA Study [18]	NA	90 – NA	ICD-10	No	Yes	6	48
Bronx Aging Study [19]	NA	90 – 100	DSM-III-R	No	Yes	5.1‖	12
Rochester Study [20]	NA	90 – 99	DSM-IV	No	Yes	NA**	NA**
Munich Study [21]	91 (78.0)	90 – 99	DSM-III-R	No	Yes	1	12

*Upper age for prevalence/incidence study respectively. [‡]Sample size in prevalence study only, while sample size in incidence studies not given. [§]At baseline/death, baseline dementia prevalence is reported in Figure 1 in the article. [‖]Mean or mean ± SD. [¶]Baseline cohort in 1990–1993, first follow-up in 1993–1994 and second follow-up in 1997–1999. [#]Median. **Dementia cases were ascertained through the medical records linkage system of the Rochester Epidemiology Project; indices in the system that might indicate dementia were searched for 6 additional years (1990–1995). Abbreviations: BASE, Berlin Aging Study; CC75CS, Cambridge City over-75s Cohort Study; CSHA, Canadian Study of Health and Aging; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders, third edition revised [22]; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, fourth edition [23]; HK elderly study, Hong Kong elderly study; ICD-10, 10th revision of the International Statistical Classification of Diseases and Related Health Problems [24]; LEILA75+, Leipzig Longitudinal Study of the Aged; MMSE, Mini-Mental State Examination; MRC–CFAS, Medical Research Council Cognitive Function and Ageing Study; MRC-ALPHA Study, Medical Research Council Ageing in Liverpool Project—Health Aspects Study; NA, not available; SNS, Stockholm Nonagenarian Study.

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2.3 Summary of main findings

It was found that dementia prevalence increased steadily with advancing age, from approximately 25% in individuals aged 90-91 years to about 60% in those aged 100-102 years. The prevalence of dementia was lower in men than in women, but the incidence did not differ by sex, which could be explained by a shorter survival time in men.

Risk factors for dementia in the 90-plus population included mild impairment in cognition or functioning. Nevertheless, other risk factors of dementia in the young old, such as APOE ε4 allele, hypertension and hypercholesterolemia, had weak or no associations with dementia in the oldest old.

Neuropathologies, including the AD pathology, vascular pathology, Lewy-related pathology, hippocampal sclerosis and cerebral amyloid angiopathy, were common in the 90-plus individuals. Pathologically defined atrophy of neocortex and hippocampus were strong correlates of dementia in this age group, whereas the association between single pathology and clinical dementia appeared to be weakened at advanced age.

Structural MRI was found to be a powerful tool in distinguishing between cognitive categories in the young old, however, its utility in the oldest old population has not been systemically investigated, which is worthy of further investigations.

CHAPTER 3: AGE-ASSOCIATED DIFFERENCES ON STRUCTURAL BRAIN MRI IN NON-DEMENTED INDIVIDUALS FROM 71 TO 103 YEARS

3.1 Overview

The aim of this study (Chapter 3) was to examine non-demented brain ageing using structural MRI, with a special focus on the 90-plus population. The specific aims were to:

1. Examine age-associated differences on structural brain MRI in non-demented community dwelling individuals from 71 to 103 years;
2. Delineate the structural MRI profile of the non-demented 90-plus individuals and compare the profile with that of the younger elderly;
3. Repeat the analyses in a subgroup of high-functioning individuals who did not have any evidence of MCI.

A wide range of MRI-derived brain measures were employed, including brain volumetrics of the grey matter and white matter, cortical thickness and white matter hyperintensities (WMHs). Age-associated differences on structural brain MRI were examined by general linear models, and the comparison of the MRI profiles between those < 90 and ≥ 90 years were performed by repeated measures analysis of variance.

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Age-associated differences on structural brain MRI in nondemented individuals from 71 to 103 years

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ABSTRACT

Successful brain aging in the oldest old (≥90 years) is underexplored. This study examined cross-sectional brain morphological differences from 8th to 11th decades of life in nondemented individuals by high-resolution magnetic resonance imaging. Two hundred seventy-seven nondemented community-dwelling participants (71–103 years) from Sydney Memory and Ageing Study and Sydney Centenarian Study comprised the sample, including a subsample of 160 cognitively high-functioning elders. Relationships between age and magnetic resonance imaging–derived measurements were studied using general linear models; and structural profiles of the ≥90 years were delineated. In full sample and the subsample, significant linear negative relationship of gray matter with age was found, with the greatest age effects in the medial temporal lobe and parietal and occipital cortices. This pattern was further confirmed by comparing directly the ≥90 years to the 71–89 years groups. Significant quadratic age effects on total white matter and white matter hyperintensities were observed. Our study demonstrated heterogeneous differences across brain regions between the oldest old and young old, with an emphasis on hippocampus, temporoposterior cortex, and white matter hyperintensities.

1. Introduction

The oldest old (OO), defined as people aged 90 years and above, are the fastest growing sector of the population internationally (Slavin et al., 2013). Although the prevalence of dementia increases steadily with age, reaching as much as 42%–76% among centenarians, the absence of dementia can serve as one indicator of successful aging (Yang et al., 2013). Only a few neuroimaging studies with adequate numbers of the OO (Barkhof et al., 2007; Beeri et al., 2011; Erten-Lyons et al., 2013; Kawas et al., 2013; Lopez et al., 2014; Polvikoski et al., 2010) are currently available; however, little is known of the "successfully" aged brains in the 10th and 11th decades of life.

Current understanding of normal brain aging is mainly based on relatively "young" elderly, yielding a nonlinear and heterogeneous pattern of brain loss (Fjell et al., 2014; Fox and Schott, 2004; Hedman et al., 2012). Most of the longitudinal (Driscoll et al., 2009; Fjell et al., 2013; Raz et al., 2005; Storsve et al., 2014) and cross-sectional (Fjell et al., 2009; Raz et al., 2004; Walhovd et al., 2011) studies agree on a "frontotemporal" pattern from 70 years and onward in healthy subjects, that is, greatest age-related brain loss being in frontal cortices and the medial temporal lobe. Accelerated age slopes of normal brain aging, from longitudinal observations, are mostly seen in hippocampus and entorhinal cortex (Fjell et al., 2012; Raz et al., 2005, 2010; Scahill et al., 2003), and some report in the occipital (Storsve et al., 2014) and orbitofrontal cortices (Driscoll et al., 2009).

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However, findings in the "young" old (YO), defined as 70–89 years, may not be applied to the OO for a few reasons. First, the concept of normal aging becomes more ambiguous at advanced age, where mild levels of cognitive impairment are commonplace and indeed "normative" (Slavin et al., 2013; Yang et al., 2013). Second, individual variability on structural magnetic resonance imaging (MRI) has been recognized in the process of brain aging (Raz et al., 2005, 2010), and is associated with subsequent cognitive trajectory (Tisserand et al., 2004). Those who age successfully into the 10th decade of life may thus have a distinct profile compared to young elderly. Third, both neurodegeneration and cerebral small vessel disease are commonly observed in nondemented nonagenarians (Savva et al., 2009; Yang et al., 2013). Therefore, it is not known if the same pattern of brain aging extends into the 90s and beyond, and whether the magnitude of age effects is maintained.

In this study, we examined the relationships between age and MRI-derived brain measures in a sample of nondemented community-dwelling individuals, aged from 71 to 103 years. Since our focus was on the OO population, and since there is no consensus in discriminating normal from mild cognitive impairment in the OO (Yang et al., 2013), we did not exclude participants with mild level of cognitive impairment from the main analyses. However, a subsample of high-functioning individuals that did not have any impairment on cognitive tests was also examined, so as to examine the relationship of the brain MRI measures with age in truly "successfully" aged individuals.

2. Methods

2.1. Participants

The selection of the study cohort is summarized in the flowchart in Supplementary Fig. 1. Participants were drawn from 2 community-based longitudinal studies: the Sydney Centenarian Study (SCS) and Sydney Memory and Ageing Study (MAS), details of which have been published previously (Sachdev et al., 2010, 2013). The YO (N = 234) were participants in MAS at baseline (Sachdev et al., 2010). Individuals aged 90–103 years (OO, N = 89) were recruited from the baseline cohort of SCS (Sachdev et al., 2013) and follow-up cohorts of MAS (Sachdev et al., 2010). OO participants from MAS with multiple waves of data were included only at their latest assessment, when at their oldest. Exclusion criteria were brain infarct (longest diameter > 2 cm) detected on MRI (N = 5, including OO n = 2), diagnosis of dementia (N = 14 in OO), other diagnosed diseases of central nervous system (Parkinson's disease, epilepsy, psychotic disorders including ongoing depression) or progressive malignancy (N = 2 in YO). Individuals with excessive movement during MRI or unsatisfactory neuroimaging quality were also excluded (N = 32, including OO n = 6).

2.2. Standard protocol approvals, registrations, and participant consent

Both the MAS (HREC09382) and SCS (HC12313) were approved by the Human Ethics Committees of UNSW Australia and the South Eastern Sydney and Illawarra Area Health Service. All participants gave written informed consent to the study before the investigation.

2.3. Categorization of cognitive status

All participants received comprehensive assessments, with different neuropsychological batteries being used for MAS (Sachdev et al., 2010) and SCS (Sachdev et al., 2013). Cognitive categories were determined by a panel comprising an old age psychiatrist, a neuropsychiatrists, neuropsychologists, and clinical psychologists based on: (1) detailed written comments from our trained research psychologist in relation to participants' performance; (2) the individual's test scores of the neuropsychological battery encompassing premorbid intelligence, attention/processing speed, memory, language, visuospatial ability, and executive function; (3) quantitative informant questionnaires including the short form of the Informant Questionnaire on Cognitive Decline in the Elderly (Short IQ CODE; Jorm, 1994) and the Bayer activities of daily living scale (Hindmarch et al., 1998). Defining cognitively high functioning in both YO and OO was based on individuals' intact neuropsychological performance across all tested cognitive domains (i.e., within 1.5 standard deviations [SDs] of normative values) and a preserved level of functioning on Bayer activities of daily living scale. These criteria (Winblad et al., 2004) would exclude any individuals with mild cognitive impairment from the subsample. The diagnosis of dementia (for exclusion purpose) was based on the Diagnostic and Statistical Manual of Mental Disorders, fourth edition criteria. Normative data from the 90+ study (Whittle et al., 2007) was used for the Boston Naming Test (Mack et al., 1992), letter fluency and animal fluency (Tombaugh et al., 1999), and Mini-Mental State Examination (MMSE; Folstein et al., 1975); performance on the remainder of the tests was judged against the next oldest available normative values for the OO. Twenty-two SCS participants had only completed the Addenbrooke's Cognitive Examination Revised (Mioshi et al., 2006) and could not tolerate a more detailed assessment, their performance was compared against the mean and SD of the high-functioning SCS participants who had completed the full neuropsychological battery.

2.4. MRI data acquisition and processing

MRI scans were acquired using Philips 3T Achieva Quasar Dual scanner (Philips Medical Systems, Best, The Netherlands) located at Neuroscience Research Australia, Sydney with acquisition parameters for T1-weighted sequence as follows: repetition time = 6.39 ms, echo time = 2.9 ms, flip angle = 8°, matrix size = 256 × 256, field of view = 256 × 256 × 190, and slice thickness = 1 mm with no gap in between, yielding 1 × 1 × 1 mm^3 isotropic voxels. T2-weighted fluid-attenuated inversion recovery (FLAIR) images were acquired (repetition time = 10,000 ms, echo time = 110 ms, inversion time TI = 2800 ms; matrix size = 512 × 512; slice thickness = 3.5 mm with no gap between slices, yielding spatial resolution of 0.488 × 0.488 × 3.5 mm^3 per voxel) to estimate the accumulation of white matter hyperintensities (WMHs).

T-1 weighted sequence imaging was processed with FreeSurfer v5.3.0 (http://surfer.nmr.mgh.harvard.edu/) at the Neuroimaging Laboratory, Centre for Healthy Brain Ageing (CHeBA), UNSW Australia. The surface reconstruction and segmentation procedures were processed automatically, yielding a surface map of cortical thickness for each person at each point (Fischl et al., 2002, 2004); data were further extracted into 34 cortical regions of interest (ROIs) using the Desikan-Killiany Atlas (Desikan et al., 2006) as previously described. Total and lobar brain gray matter (GM), white matter (WM) as well as total ventricular volumes were calculated from volumes of generated segmentations by FreeSurfer (Fischl et al., 2004; Salat et al., 2009a). The estimated volumes of WM included WMHs. Following the automatic procedure, accuracy of the spatial registration and tissue segmentation steps were inspected visually for errors. Typical errors, especially in the OO, that most commonly required manual editing comprised wrongly segmented subcortical WMHs, inclusion of dura or vessels to the cortex and failed intensity normalization. These errors were manually corrected using TKMEDIT toolbox in FreeSurfer on all OO, as well as 34% (N = 81) of the YO subjects who presented with

extensive WMHs or problematic values on cortical thickness. A final quality inspection after editing was conducted, and the MRI imaging of subjects were classified as pass (N = 268), fail (N = 32), or partial (N = 9). Passed MRI data were included for surface- and ROI-based analysis. A "partial" rating referred to having less than 5 of 34 ROIs that produced inaccurate cortical reconstruction, and only data of the good quality regions was used for ROI-based analysis. Participants with failed MRI quality were excluded.

For subcortical volumes, T1-weighted MRI data were processed with the FMRIB Software library (FSL) v5.0.1 (Jenkinson et al., 2012); and 7 subcortical ROIs per hemisphere were generated using FMRIB's Integrated Registration and Segmentation Tool (Patenaude et al., 2011). Values beyond 1.96 SD in the YO and results of all the OO had been visually inspected applying the ENIGMA protocols (http://enigma.ini.usc.edu/protocols/imaging-protocols/) to ensure accuracy. We combined the volume of caudate and accumbens into one ROI as "caudate-accumbens" to achieve better accuracy due to indistinct boundaries between these 2 structures in a considerable proportion of cases. Values of subcortical ROIs were excluded if they failed visual quality inspection, and missing data were mostly seen in amygdala, putamen, and pallidum due to underestimation of the ROI volume.

Accumulation of the WMHs was estimated using our previously established method (Wen and Sachdev, 2004). Briefly, both the T1 and FLAIR images were coregistered and normalized into the Talairach space, and WMHs were identified and extracted by an algorithm implemented in Matlab based on the signal intensities on FLAIR images. WMHs within a predefined rim 7.5–10 mm from the ventricles were considered as periventricular WMHs; whereas, the rest of the WMHs, that is, the deep WMHs, were further divided into lobar WMHs using a standard atlas (Duvernoy, 1991). Visual inspection was applied on the WMHs output in all OO and randomly selected 20 YO participants, and only 5 subjects required minor manual correction using the FSLVIEW toolbox within the FSL v5.0.1 (Jenkinson et al., 2012). Five participants in MAS did not have FLAIR imaging data.

2.5. Data conditioning

Before conducting the main analyses, neuroimaging data were examined for reliability and potential systematic bias. Hippocampal volumes, generated by both FreeSurfer and FSL, were compared with manual tracing in 85 participants (70–91 years). The intraclass correlation coefficient indicating the level of agreement between volumes obtained by FSL and manual tracing (0.67, 95% confidence interval: 0.54–0.77, $F = 5.11$, $p < 0.01$) is higher than that between volumes obtained by FreeSurfer and manual method (0.46, 95% confidence interval: 0.28–0.62, $F = 2.73$, $p < 0.01$). Although FSL overestimated hippocampal volume compared with manual tracing (mean ± SD in mm^3: 3402 ± 434 vs. 2361 ± 333, respectively), no significant correlation was found between the FSL/manual ratio and age ($r = -0.03$, $p = 0.80$), suggesting that the degree of overestimation is not associated with age.

The Pearson correlation between the left and right measures of each ROI was used as a surrogate of data reliability in the total sample. The left-right correlation coefficients were high in both YO and OO for global measures (r = 0.88–0.98), that is, for total GM, total subcortical volume, mean thickness and total WMHs. Individual ROIs were found to have more variability, with median correlation coefficient r = 0.63 for the YO and median r = 0.61 for the OO. A number of ROIs had left-right correlation coefficients less than 0.5 either in YO or OO, including the cingulate, frontal pole, and regions with small surface or volume: banks of superior sulcus ($r_{YO} = 0.42$, $r_{OO} = 0.45$), caudal anterior cingulate ($r_{YO} = 0.27$, $r_{OO} = 0.38$), posterior cingulate ($r_{YO} = 0.46$, $r_{OO} = 0.52$), rostral anterior cingulate ($r_{YO} = 0.39$, $r_{OO} = 0.57$), frontal pole ($r_{YO} = 0.39$, $r_{OO} = 0.56$), and the amygdala ($r_{YO} = 0.23$, $r_{OO} = 0.34$). Only 3 of the ROIs had a statistically significant difference in correlations coefficients between the YO and OO groups ($p < 0.05$ after Bonferroni correction): rostral anterior cingulate ($r_{YO} = 0.39$ vs. $r_{OO} = 0.57$), temporal pole ($r_{YO} = 0.39$ vs. $r_{OO} = 0.68$), and the caudate-accumbens ($r_{YO} = 0.88$ vs. $r_{OO} = 0.56$).

The previously mentioned analysis suggests a reasonable data quality for most of the brain measures. However, results for the cingulate cortex, in particular the anterior cingulate, frontal and temporal polar cortices, as well as the amygdala and caudate-accumbens may need to be interpreted with caution. It should also be noted that there was no tendency for smaller or larger correlations to be found in either the YO or OO samples, so these results do not suggest higher or lower reliabilities for the brain measures in either of the groups.

2.6. Statistical analyses

Two types of general linear models (GLMs) were used in exploring the effects of advanced age on structural brain MRI. Surface- and ROI-based analyses were performed with FreeSurfer (www.surfer.nmr.mgh.harvard.edu) and SPSS Statistics version 21.0 (SPSS, Chicago, IL, USA), respectively. Cross-sectional estimates of the age effects across cortical mantle were analyzed using vertex-based GLMs with age as the predictor variable adjusted for sex. Generated brain maps were projected on a semi-inflated template brain using a circularly symmetric Gaussian kernel with a full width at half maximum at 20 mm. The statistical significance was re-thresholded by a conventional criterion for correction for multiple testing (false discovery rate [FDR] corrected $p < 0.05$; Genovese et al., 2002).

For ROI-based analyses, ROIs values of left and right hemispheres were combined to reduce the number of comparisons and to increase the estimation reliability (Fjell et al., 2012). Both linear and quadratic relationships of age with brain measures were explored using age and age^2 as the predictor variables, adjusted for sex, as well as the estimated intracranial volume (eTIV) if a brain volume was the dependant variable. Age was centered to reduce the multicollinearity. The moderating effect of sex on the relationship between age and brain measures was also examined by the inclusion of an age by sex interaction term in the models. Natural log transformation of the dependent variable—volumes of WMHs—was carried out to reduce the skewness (<1 after transformation) to allow analysis with parametric statistical procedures. Quadratic effects of age on WMHs were also examined without logarithmic transformation of the volumes to check that any observed nonlinearity was not influenced by the logarithmic transformation. To test equality of the regression coefficients of age in the linear model, the interaction between the age and selected ROIs (defined as within-subjects factor) were examined using repeated measures analysis of covariance (ANCOVA). An α-level of $p < 0.05$ was used after correction for FDR (Benjamini and Hechtlinger, 2014) unless stated otherwise. Other potential confounders that were initially examined in the univariate GLMs included education, APOE ε4 carriage status, and the presence of vascular risk factors. Since repeating the GLMs with the inclusion of each of these potential confounders did not produce substantial change of the magnitude of age effects (<10%) or the p-values of the predicting variables—age and age^2, they were not included in the models reported.

Repeated measures ANCOVA were also carried out to compare the structural profile of the OO to YO participants. We defined the age group (OO vs. YO) as the between-subjects factor and a set of brain ROIs as within-subjects variables. Sex was included in the

models as a covariate, as well as eTIV if the dependent variables were volumetrics. Interactions of age group by brain ROIs were examined to investigate whether differences in brain measures between the OO and YO groups were greater for some ROIs than for others.

To allow meaningful comparisons between different brain regions regarding differences with age, the original brain measures were transformed to normalized scores by dividing by the mean value of the brain measure in the nondemented YO group, with the transformed measure being presented as a percentage. Thus, differences with age in the transformed MRI measures are expressed relative to their mean values in the nondemented younger group. Note that, for any particular brain region, this represents only a linear transformation of the original variable, so results of all statistical tests remain unchanged, although the values of effect strengths will change due to change in the units of measurement.

3. Results

The final cohort comprised 277 nondemented participants, of which sample characteristics are shown by age group and cognitive category in Table 1. Demographics were comparable for YO and OO with the exception of MMSE (Folstein et al., 1975) being significantly lower in the OO compared to YO in the total sample and high-functioning subsample. The OO participants had a significantly higher prevalence of cerebral vascular disease and transient ischemia attack, and a significantly lower prevalence of dyslipidemia compared to the YO in both the total and high-functioning samples.

Demographics of the included MAS participants in the present study were not different from the baseline sample of MAS apart from the expected higher mean age in the former group (mean ± SD: 80.1 ± 5.8 vs. 78.7 ± 4.8 years, F = 14.07, $p < 0.01$). Participants drawn from the SCS had higher MMSE scores (mean ± SD: 27.2 ± 2.1 vs. 25.4 ± 3.0, F = 13.44, $p < 0.01$) as well as less proportion of female (43.2% vs. 66.5%, $\chi^2 = 7.42$, $p < 0.01$) compared with the nondemented SCS subjects at baseline that were not included in the present study.

3.1. Global and subcortical brain volumetrics

Significant linear relationships of age with brain volumetrics were seen across all the brain areas in the total sample, after controlling for sex and eTIV (Table 2). As can be seen from inspection of the regression coefficients for normalized values (expressed as a %) of the brain volume measures, the estimated relationships with age differed across regions. Of particular interest is that age had a stronger negative relationship with hippocampal volume than with total GM (B's = −8.96% vs. −5.30%, F = 24.10, $p < 0.05$). No significant difference in relationships with age was found between total GM and WM in the linear model.

In the total sample, quadratic effects of age were statistically significant for total WM volume (t = 3.12, $p < 0.01$) and the logarithmically transformed deep WMHs volume (t = 3.06, $p < 0.01$). For WM volume, the quadratic effect represented a weaker negative relationship with age at higher ages, with estimated slopes of −6.93 and −2.41 normalized score units per decade at 80 years and 90 years, respectively. In contrast, the positive effect of age on deep

Table 1
Sample characteristics

Age range, y	Total sample			High-functioning subsample		
	70–89	90+	p[a]	70–89	90+	p[a]
N	207	70	—	117	43	—
Age, years (mean ± SD)	**78.7 ± 4.4**	**95.4 ± 3.5**[b]	<0.01	**78.6 ± 4.3**	**96.6 ± 3.1**	<0.01
Female, %	52.2	48.6	0.55	55.6	46.5	0.31
Education, years (mean ± SD)	12.2 ± 3.5	11.3 ± 3.8	0.06	12.4 ± 3.8	11.5 ± 3.6	0.21
MMSE[g] (mean ± SD)	**28.2 ± 1.5**	**27.3 ± 2.0**	<0.01	**28.5 ± 1.2**	**27.8 ± 1.4**	<0.01
APOE ε4 carriage, %	24.0[b]	15.2[c]	0.13	20.7[d]	12.2[f]	0.23
High-functioning, %	56.2	61.4	0.47	—	—	—
MCI, %	30.0	37.1	0.26	—	—	—
Vascular risk factors[h], %						
CVA	**1.5**[b]	**8.7**[d]	<0.01	**0.9**[f]	**9.5**[d]	<0.01
TIA	4.5[e]	10.6[c]	0.07	2.6[c]	9.8[f]	0.06
CAD	**10.7**[d]	**21.2**[c]	0.03	**9.5**[d]	**22.5**[b]	0.03
HTN	56.3[d]	60.9[d]	0.51	54.7	61.9[d]	0.42
Cholesterol	**54.4**[d]	**42.4**[c]	0.02	**62.9**[d]	**32.5**[b]	<0.01
DM	9.2	10.0	0.84	6.0	7.0	0.82
Smoking	53.9[d]	42.0[d]	0.09	53.8	46.5	0.41
Depression	15.5[d]	7.4[f]	0.09	17.2[d]	7.3[f]	0.12
Descriptive statistics, mean ± SD						
Total GM, cm^3	**528.4 ± 49.1**	**474.9 ± 37.1**	<0.01	**533.6 ± 48.6**	**477.8 ± 37.6**	<0.01
Total WM, cm^3	**427.6 ± 53.9**	**387.4 ± 45.5**	<0.01	**430.0 ± 53.5**	**390.6 ± 45.4**	<0.01
Total WMHs, cm^3	**12.1 ± 9.8**	**32.2 ± 18.3**	<0.01	**12.5 ± 9.9**	**33.3 ± 18.0**	<0.01
Hippocampus, cm^3	**6.82 ± 0.81**	**5.67 ± 0.75**	<0.01	**6.94 ± 0.81**	**5.77 ± 0.73**	<0.01
Mean cortical thickness, mm	**2.32 ± 0.10**	**2.21 ± 0.11**	<0.01	**2.34 ± 0.09**	**2.21 ± 0.11**	<0.01

Bold values indicate significant differences ($p < 0.05$) between age groups within the same cognitive category.
Key: ANOVA, analysis of variance; APOE, apolipoprotein; CAD, coronary artery disease; CVA, cerebral vascular accident; DM, diabetes mellitus; GM, gray matter; HTN, hypertension; MCI, mild cognitive impairment; MMSE, mini-mental status examination; SD, standard deviation; TIA, transient ischemic attack; WM, white matter; WMHs, white matter hyperintensities.
[a] Test-wise *p*-value of one-way ANOVA or Pearson χ^2 test.
[b] Number of missing data, b = 3.
[c] Number of missing data, c = 4.
[d] Number of missing data, d = 1.
[e] Number of missing data, e = 5.
[f] Number of missing data, f = 2.
[g] MMSE scores were prorated from raw scores with no adjustment for age, English-speaking background or education; all participants completed more than 27/30 of the MMSE scoring items.
[h] Vascular risk factors are based on self-reported medical history.

Table 2
Relationship of age with brain volumetrics

Brain volumetrics	Total sample			High-functioning subsample		
	N	B[a] (SE), cm^3	B[b] (SE), %	N	B[a] (SE), cm^3	B[b] (SE), %
Total						
Total gray matter	277	**−27.98 (1.99)**	**−5.30 (0.28)**	160	**−28.78 (2.38)**	**−5.45 (0.45)**
Total white matter[d]	274	**−18.70 (2.38)**	**−4.37 (0.56)**	157	**−18.01 (2.96)**	**−4.21 (0.69)**
Total ventricle	277	**8.83 (1.03)**	**21.75 (2.55)**	160	**8.72 (1.42)**	**21.47 (3.50)**
Subcortical						
Hippocampus	272	**−0.61 (0.06)**	**−8.96 (0.84)**	157	**−0.58 (0.07)**	**−8.55 (1.03)**
Putamen	236	**−0.74 (0.09)**	**−8.91 (1.05)**	137	**−0.76 (0.11)**	**−9.24 (1.30)**
Pallidum	239	**−0.30 (0.05)**	**−9.69 (1.74)**	136	**−0.29 (0.07)**	**−9.24 (2.29)**
Thalamus	272	**−0.98 (0.08)**	**−7.71 (0.65)**	158	**−0.96 (0.10)**	**−7.52 (0.81)**
Caudate-accumbens	269	**−0.36 (0.06)**	**−4.99 (0.80)**	157	**−0.38 (0.07)**	**−5.23 (0.92)**
Amygdala	241	**−0.08 (0.04)**	**−3.42 (1.66)**	141	−0.07 (0.05)	−3.20 (2.18)
WMHs[c]						
Ln (periventricular WMHs)	272	**0.27 (0.05)**	**0.27 (0.05)**	159	**0.26 (0.05)**	**0.26 (0.05)**
Ln (deep WMHs)[d]	272	**0.78 (0.07)**	**0.78 (0.07)**	159	**0.74 (0.08)**	**0.74 (0.08)**

Estimates of age-related differences per decade on brain volumetrics are presented within the total sample and the high-functioning subsample respectively, after adjusting for sex and estimated intra-cranial volume (eTIV) in univariate general linear models.
Bold values indicate $p < 0.05$ (of 2-tailed t test) after corrected for multiple testing using False Discovery Rate (FDR).
Key: SE, standard error; WMHs, white matter hyperintensities.
[a] B regression coefficients representing relationships with age of brain volumes in cm^3 per decade.
[b] B regression coefficients representing relationships with age of brain volumes in normalized scores per decade.
[c] WMHs values are logarithmically transformed.
[d] Marked brain volumetrics were found to have significant quadratic age effects, and separate analyses are described in the main text.

WMHs was found to be greater at older ages, with estimated effects of age of 31.83 and 144.31 normalized scores per decade at 80 years and 90 years, respectively. The slope estimates of WMHs were obtained from results using log WMHs as the DV, and back transforming slope estimates using the exponential function. When this analysis was repeated without the logarithmic transformation of WMHs, significant quadratic effects were again obtained, that similarly represented a stronger positive relationship with age at higher values of age. A test-wise significant quadratic effect of age was also observed for the putamen ($t = -2.15$, test-wise $p = 0.03$), with the estimated effects of age in normalized score units being −5.7 and −11.66 per decade at 80 years and 90 years, respectively. However, this quadratic effect was not significant after FDR correction for multiple testing. Scatter plots with the estimated fits for selected brain structures are show in Fig. 1, in which periventricular and deep WMHs were combined into total WMHs.

When the previously mentioned analyses were repeated in the high-functioning subsample, similar patterns of relationships with age were observed. In the analyses using either the full sample or the high-functioning subsample, no significant age by sex interactions were found for global or subcortical volumetrics.

Group comparisons between the YO and OO of brain volumetrics for GM, WM, subcortical structures and WMHs, and their subdivided ROIs, are presented in Fig. 2. Normalized brain volumes are used to facilitate comparisons of brain regions of different sizes. In the total sample, significant YO-OO differences were found in all the brain volumetrics ($t = 2.56–10.94$ for GM, WM, and subcortical measures and $t = -13.48$ to -3.92 for WMHs volumes, $p < 0.05$) except for the amygdala ($t = 0.68$, test-wise $p = 0.50$) after controlling for sex and eTIV. In the high-functioning subjects, no significant difference between YO and OO were found in insula WM volume ($t = 1.76$, test-wise $p = 0.08$) as well as all subcortical volumetrics ($t = -0.46$ to 1.92, test-wise $p = 0.06–0.64$) except for hippocampus ($t = 2.77$, $p = 0.04$). Multivariate tests for age group by ROIs interaction using the repeated measures ANCOVA procedure were significant (Pillai's trace = 0.05–0.52, $F = 2.43–56.42$, $p < 0.05$) for all 4 sets of the brain ROIs, indicating that the differences between YO and OO were heterogeneous within each set of the brain volumetrics. Most notably (Fig. 2A), the YO-OO differences were more pronounced in the temporal ($F = 5.76$, $p = 0.02$) and occipital GM ($F = 6.31$, $p = 0.02$) compared to that in total GM volume, whereas it was the opposite in the frontal ($F = 8.37$, $p < 0.01$) and insula GM ($F = 23.37$, $p < 0.01$). For subcortical volume (Fig. 2C), although test-wise significant smaller YO-OO differences were noted in thalamus ($F = 5.62$, test-wise $p = 0.02$) and in amygdala ($F = 4.57$, test-wise $p = 0.03$) compared to hippocampus, they became nonsignificant (both $p = 0.09$) after FDR correction. Accumulation of the WMHs in the OO were mostly seen in the deep WMHs ($F = 241.17$, $p < 0.01$), in particular deep WMHs of the frontal, temporal, and parietal lobe ($F = 149.18$, 183.52, and 82.47, all $p < 0.01$) relative to that seen in YO (Fig. 2D).

3.2. Cortical thickness

Surface-based analyses in the total sample revealed significant age effects on cortical thickness in most of the cortex, especially in the entorhinal, transverse and superior temporal, precentral, precuneus, superior parietal, and lateral occipital cortices; whereas, the effects of age were nonsignificant in part of the middle and inferior frontal gyrus, frontal pole, insula, and inferior temporal gyrus (Fig. 3). Comparable pattern was observed in the high-functioning subjects, except for minor discrepancies noted in the prefrontal and insula areas which seemed to be more "preserved" in the high-functioning subgroup. There was some "thickening" with age, mainly in the anterior cingulate in both samples and in a small area of the right insula in high-functioning subjects.

Linear relationships of age with cortical ROIs are presented in Table 3. Cortical thickness in all except 4 ROIs (rostral, middle frontal, frontal pole, and anterior cingulate) was significantly associated with age (FDR corrected $p < 0.05$), with the entorhinal cortex being the most age-sensitive ROI (−7.031 normalized score units per decade). Not only were the patterns of age-related difference similar between the total sample and the high-functioning subsample in ROI-based analyses, but the topographic distribution of age effects in ROI-based analyses were also comparable to that of the surface-based analyses. However, there was no significant age-related "thickening" in any cortical ROIs. Test-wise significant interactions (test-wise $p < 0.05$) between age and sex were observed in a few ROIs (lateral occipital, posterior cingulate, cuneus,

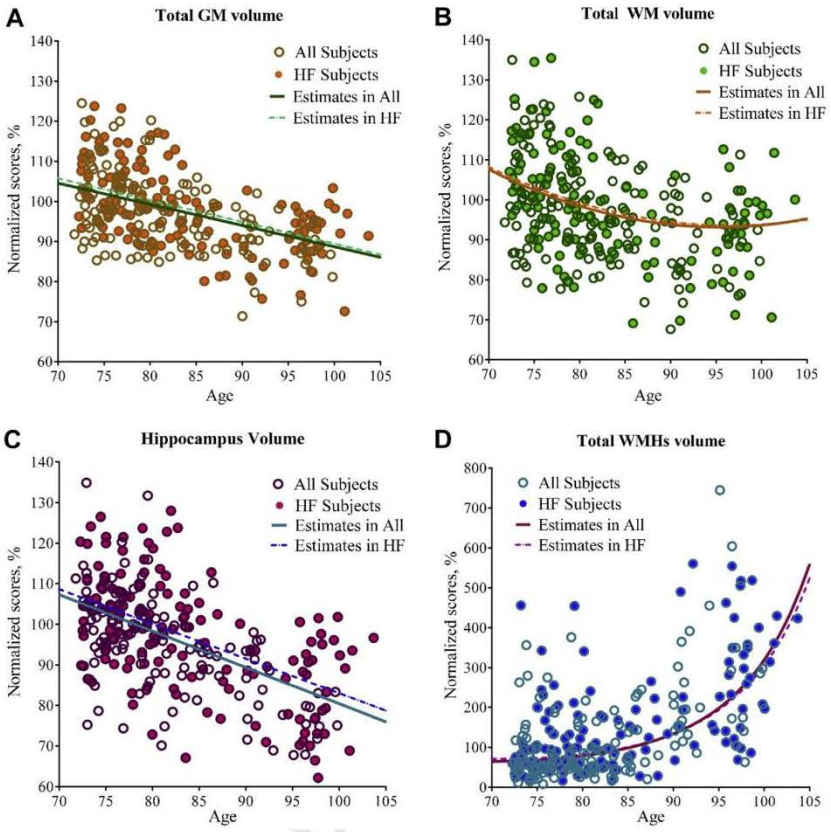

Fig. 1. Relationship of age with total brain volumes from 71 to 103 years. (A–D) The panels A–D show the individual data plots as well as the cross-sectional estimated fit(s) as a function of age for total gray matter (GM), white matter (WM), and hippocampal volumes, as well as total white matter hyperintensities (WMHs) in the total sample and the high-functioning (HF) subsample. Values are presented in normalized values (expressed as a %). Note that panel D plots the estimated fit of regression of Ln (total WMHs) on age with total WMHs displayed in original units after back transformation using the exponential function. All the estimated fits are adjusted for sex and estimated intracranial volume.

temporal pole, and pericalcarine cortices), yielding a steeper age slope in women than in men with the exception of posterior cingulate being the opposite. Yet, none were significant after FDR correction (Supplementary Table 1).

The profile of cortical ROIs in the OO comparing to YO is presented in Fig. 4. In both samples, the YO and OO differed significantly ($t = 3.26–10.46$, $p < 0.05$) on cortical thickness of all ROIs with the exception in anterior cingulate (caudal and rostral) and frontal pole, after controlling for sex. A multivariate test using the repeated measures ANCOVA procedure of the age group by ROIs interaction was significant (Pillai's trace = 0.38, $F = 4.07$, $p < 0.01$), suggesting that the differences between YO and OO were heterogeneous across the cortical mantle. Entorhinal, transverse temporal, superior temporal, superior parietal, precuneus, and precentral cortices had significantly larger YO-OO difference ($F = 11.47–21.11$, $p < 0.05$) compared to the YO-OO difference seen in mean cortical thickness; whereas middle temporal, posterior cingulate, inferior frontal gyrus, anterior cingulate, rostral middle frontal, as well as frontal polar cortices were noted to be more "preserved" ($F = 5.49–23.06$, $p < 0.05$) relative to the average.

4. Discussion

To our knowledge, this is the first study to examine age-related differences on structural brain MRI in a nondemented sample from the 8th to 11th decades of life. Linear relationships of age with brain measures were found for cortical and subcortical GM and total ventricle volume; whereas quadratic effects of age were observed for total WM and deep WMHs volumes. Effects of advanced age were greatest in the medial temporal lobe and parietal and occipital cortices, as well as in deep WMHs; whereas, select cortical (prefrontal, insula, and anterior cingulate) and subcortical (accumbens-caudate and amygdala) regions were relative "preserved" compared to the overall age effect on the brain.

Both a nondemented sample and a high-functioning subsample were used in the present study. As normal aging per se is associated with progressive cognitive decline (Singer et al., 2003), it is not unexpected to have mild level of cognitive impairment when an individual lives long enough (Bullain and Corrada, 2013; Fjell et al., 2014; Yang et al., 2013). The subgroup of high-functioning individuals represents a further selected population of "successfully" aged individuals, who did not have any evidence of cognitive

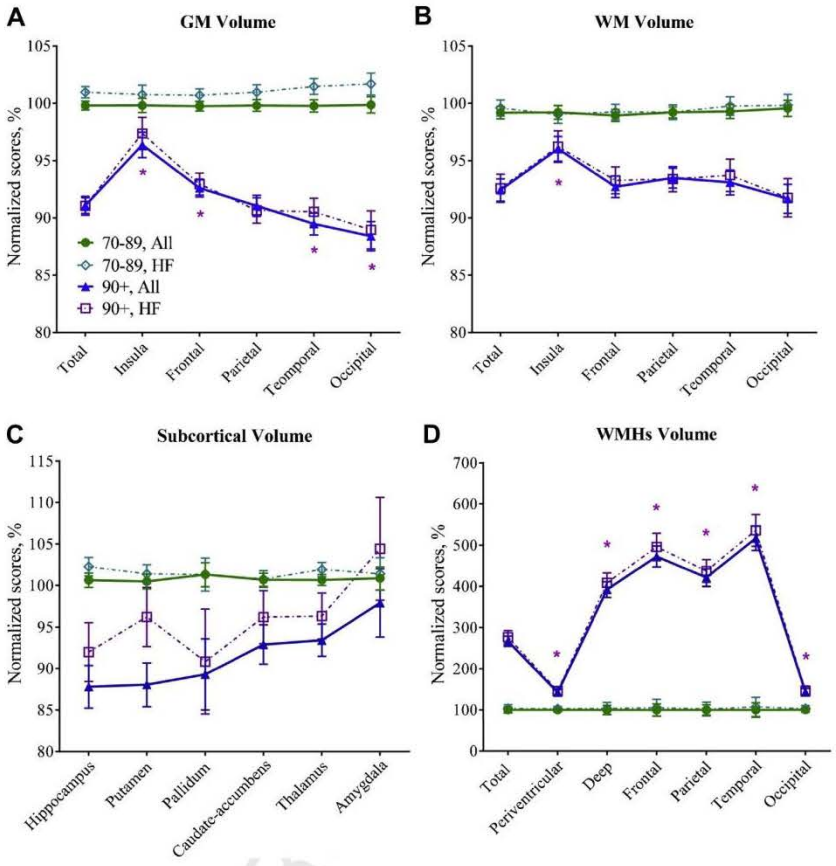

Fig. 2. Group comparison of brain volumetrics between the young old (YO, 70–89 years) and oldest old (OO, 90+ years). The estimated mean and standard errors of the brain regions of interest (ROIs) are presented in normalized values (expressed as a %) by age group and cognitive category, after adjusting for sex and estimated intracranial volume in repeated measures ANCOVA. In the total sample, significant larger or smaller YO-OO differences ($p < 0.05$ after false discovery rate correction) compared to the first brain volumetric (i.e., the total GM, total WM, hippocampus, and total WMHs volume) of the each figure are marked with "*". Abbreviations: ANCOVA, analysis of covariance; GM, gray matter; HF, high-functioning subsample; WM, white matter; WMHs, white matter hyperintensities.

impairment. Both samples presented with similar patterns of age effects on structural brain MRI, suggesting that results for the whole sample were not substantially influenced by the inclusion of individuals with mild level of cognitive impairment. Moreover, our participants are generally in better physical and cognitive health, and able to withstand a brain MRI, compared to their peers. The included OO are, in particular, subject to this "health" bias when compared to a population-based sample (Borjesson-Hanson et al., 2004; Whittle et al., 2007); and this needs to be taken account in the interpretation of the pattern observed.

Substantial similarities, but also important differences, can be seen between our results and reports on healthy younger populations. The magnitude of the age trends in total GM and hippocampal volumes in this study are generally comparable to those reported in younger healthy samples. In a cross-sectional sample of 883 individuals aged from 18 to 94 years, the reported age-related variation in the total cortical volume are approximately linear from 50 to 79 years, and their estimated magnitude of age effect is similar to our findings (Walhovd et al., 2011). As for from 80 years onward, previous cross-sectional estimates of the associations between total cortical volume and age are, however, small and inconsistent relative to that observed in younger individuals, probably due to limited sample sizes (Jernigan et al., 2001; Walhovd et al., 2005, 2011). Relationship of hippocampal volume with age is found to be strong from 60 years onward, and its magnitude has been found to be greater than that of the total cortical volume (Raz et al., 2004; Walhovd et al., 2011), in agreement with our results. Findings from the present study suggest that advanced age is associated with significantly smaller GM and hippocampal volumes, with a continuous age trend similar to that observed in the young elderly. In longitudinal studies (with $N \geq 50$ and mean age $\geq$70 years), the estimated rates of total brain atrophy range from 5.0% to 7.7% per decade (Driscoll et al., 2009; Goldstein et al., 2005; Resnick et al., 2003; Silbert et al., 2008), with the exception of one study which reported rates of atrophy as large as 21.0% per decade in participants in their 80s (Tang et al., 2001). Moreover, many longitudinal studies revealed accelerated atrophy in both total GM volume and hippocampus from age 60 years onward (Driscoll et al., 2009; Hedman et al., 2012; Raz et al., 2005, 2010; Scahill et al., 2003). Although the magnitude of the age

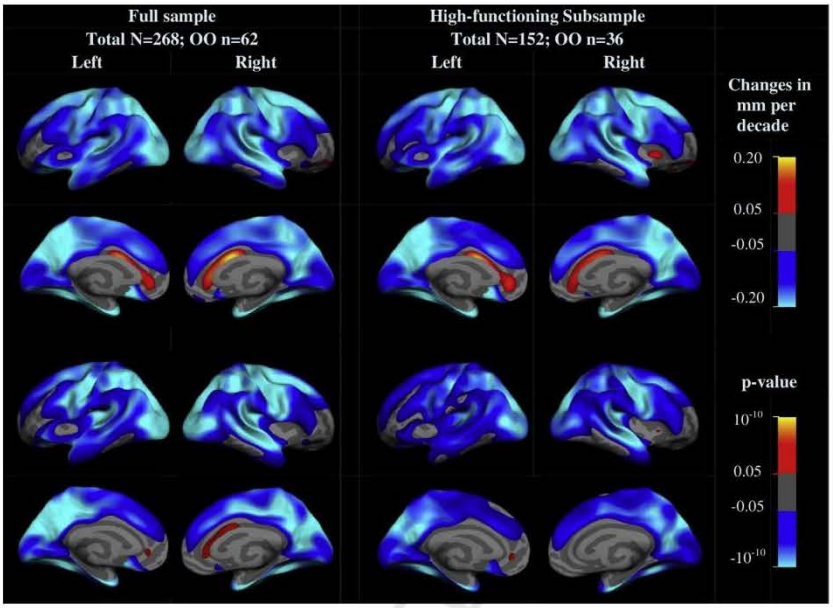

Fig. 3. Surface analysis of age effects on cortical thickness. Top: estimated age-related differences in absolute magnitude (mm per decade) in the total sample and the high-functioning subsample respectively, after controlling for sex. Blue-cyan indicates thinner cortex at higher age; red-yellow indicates the opposite. Bottom: results of general linear models testing whether age-related differences significantly differ from zero. The color scale on bottom right represents *p*-values after false discovery rate (FDR) correction for multiple testing. Blue-cyan indicates significant negative associations between cortical thickness and age; red-yellow indicates significant positive associations. Abbreviation: OO, oldest old. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

trend in our sample is similar to most of the longitudinal estimates for the young elderly, no significant quadratic effects of age were noted in any measure of the GM structures in our study. Such discrepancies are likely to be related to the cross-sectional design, the relative narrow age range as well as the potential "health" bias in this study.

Not surprisingly, considerable heterogeneity in age-related differences was observed across different brain regions. Both the surface-based analyses and YO-OO comparison suggested strong involvement in selected temporal cortices and the hippocampus. Entorhinal cortex and hippocampus are considered regions most vulnerable to decline in both normal aging and early Alzheimer's disease (AD; Fjell et al., 2012, 2013, 2014), and our data now suggest that such vulnerability extends beyond the age of 90 years. Structures involved in the default mode network have also been regarded as prime targets in both normal and pathologic aging (Buckner et al., 2008; Fjell et al., 2014). Although age effects were notable for parahippocampal, orbitofrontal, precuneus, and inferior parietal cortices, other main hubs of the default mode network (Buckner et al., 2008), including middle temporal and posterior cingulate cortices were not as much affected, in the present study.

Other prime targets associated with advanced age revealed from our sample are the occipital and parietal cortices, which include the primary somatosensory (postcentral), visual (partly the lateral occipital), and auditory cortices (superior temporal and transverse temporal). Although longitudinal studies of mid-age and young elderly found no or minor age-related cortical thinning in visual cortex (Raz et al., 2004, 2005, 2010), another longitudinal study in healthy subjects aged 23–87 years reported accelerated decline in large areas of occipital cortex(Storsve et al., 2014), which is in agreement with our findings. Similarly in cross-sectional studies, greater loss in the primary sensory and motor cortices has been associated with older age, compared to younger samples (McGinnis et al., 2011; Salat et al., 2004). Some authors have ascribed these findings to the "retrogenesis" hypothesis, with early-maturing regions of the brain being affected only during the late stage of aging (McGinnis et al., 2011). Our findings support the view that some of these early-maturing cortices experience prominent loss at advanced age. Some caution is prudent in such an interpretation, since factors other than brain developmental and involutional processes need to be considered, such as the topographic distribution of underlying neuropathologies and their contribution to cortical thinning (Jagust, 2013; Wardlaw et al., 2013).

"Accelerated" accumulation of the WMHs was noted at advanced age, in contrast to the "decelerated" age slope found in WM. The "accelerated" age trend of WMHs is consistent with longitudinal observation in a large cohort of elderly (N = 1118, 64.9–82.2 years) (Maillard et al., 2009), whereas other studies of mid-aged and "young" elder subjects report linear relationship of WMHs with age (Ikram et al., 2008; Silbert et al., 2008) or even decelerating age slope (Raz et al., 2012). These discrepancies are likely to be ascribed to sampling variation, in particular the differences in age ranges. Furthermore, we found that deep WMHs were more affected at advanced age; whereas longitudinal studies have observed more accumulation of the periventricular WMHs over time (Maillard et al., 2009; Silbert et al., 2008). Such inconsistency could be partly explained by different classifications of WMHs applied (Kim et al., 2008). Since we only define WMHs within a rim of 7.5–10 mm from the ventricles as periventricular WMHs, large confluence WMHs abut to ventricles but beyond this predefined border were partly counted as deep WMHs (Wen and Sachdev, 2004). Although WMHs are presumed to be related to cerebral

Table 3
Relationship of age with cortical thickness

ROIs[a]	Total sample		High-functioning subsample	
	N	B[c] (SE), %	N	B[c] (SE), %
Mean thickness	277	**−3.05 (0.30)**	160	**−2.98 (0.35)**
Temporal				
Entorhinal	275	**−7.03 (0.83)**	158	**−7.58 (0.97)**
Transverse temporal	277	**−5.58 (0.68)**	160	**−5.03 (0.83)**
Superior temporal	277	**−4.81 (0.39)**	160	**−4.73 (0.48)**
Parahippocampal	277	**−4.30 (0.78)**	160	**−4.03 (0.87)**
Temporal pole[b]	275	**−4.02 (0.66)**	159	**−3.29 (0.77)**
Fusiform	275	**−3.97 (0.44)**	159	**−3.58 (0.53)**
BanksSTS	277	**−3.11 (0.43)**	160	**−2.99 (0.53)**
Inferior temporal	272	**−2.41 (0.49)**	156	**−2.53 (0.62)**
Middle temporal	274	**−2.26 (0.40)**	158	**−2.37 (0.49)**
Parietal				
Precuneus	274	**−4.91 (0.40)**	158	**−5.00 (0.48)**
Superior parietal	277	**−4.62 (0.45)**	160	**−4.64 (0.56)**
Postcentral	277	**−3.48 (0.42)**	160	**−3.43 (0.53)**
Inferior parietal	277	**−3.31 (0.40)**	160	**−3.53 (0.49)**
Supramarginal	277	**−3.06 (0.40)**	160	**−3.25 (0.48)**
Isthmus cingulate	277	**−2.27 (0.64)**	160	**−2.50 (0.78)**
Posterior cingulate[b]	277	**−1.80 (0.51)**	160	**−1.92 (0.68)**
Occipital				
Lateral occipital[b]	275	**−4.44 (0.48)**	158	**−4.10 (0.59)**
Lingual	277	**−3.71 (0.48)**	160	**−3.69 (0.54)**
Cuneus[b]	277	**−3.56 (0.52)**	160	**−3.27 (0.61)**
Pericalcarine[b]	277	**−2.82 (0.50)**	160	**−3.21 (0.57)**
Frontal				
Precentral	277	**−4.27 (0.39)**	160	**−4.15 (0.49)**
Paracentral	276	**−3.83 (0.46)**	159	**−3.71 (0.58)**
Caudal middle frontal	276	**−2.94 (0.45)**	159	**−3.07 (0.56)**
Superior frontal	277	**−2.70 (0.45)**	160	**−2.43 (0.53)**
Lateral orbital frontal	274	**−2.22 (0.46)**	158	**−1.82 (0.60)**
Medial orbital frontal	274	**−2.10 (0.56)**	158	**−1.81 (0.66)**
Pars opercularis	277	**−1.72 (0.36)**	160	**−1.76 (0.42)**
Pars triangularis	277	**−1.46 (0.44)**	160	**−1.83 (0.55)**
Pars orbitalis	276	**−1.45 (0.56)**	159	**−1.63 (0.67)**
Rostral middle frontal	274	*−0.91 (0.46)*	160	*−1.11 (0.56)*
Rostral anterior cingulate	271	−0.09 (0.65)	158	−0.07 (0.79)
Caudal anterior cingulate	275	0.66 (0.79)	159	0.39 (0.97)
Frontal pole	272	0.97 (0.74)	159	0.98 (0.89)
Insula	274	**−1.87 (0.43)**	160	−2.01 (0.55)

Estimates of the linear effects of age on cortical regions of interest (ROIs) are presented within the total sample and the high-functioning subsample, respectively, after adjusting for sex. Quadratic effects of age are small and nonsignificant, thus are not shown here.

Bold values indicate $p < 0.05$ (of 2-tailed t test) after corrected for multiple testing using False Discovery Rate (FDR); and italic values indicate $p < 0.10$ (of 2-tailed t test) after FDR correction.

Key: BanksSTS, banks of superior temporal sulcus; ROIs, regions of interest; SE, standard error.

[a] Regions of interest (ROIs), grouped by lobe and sorted by size of relationships with age.

[b] Marked ROIs had test-wise significant interactions ($p < 0.05$) between age and sex within either total sample or high-functioning participants. Separate estimates of age effects in men and women are presented in Supplementary Table 1.

[c] B regression coefficients representing relationships with age of cortical thickness in normalized scores per decade.

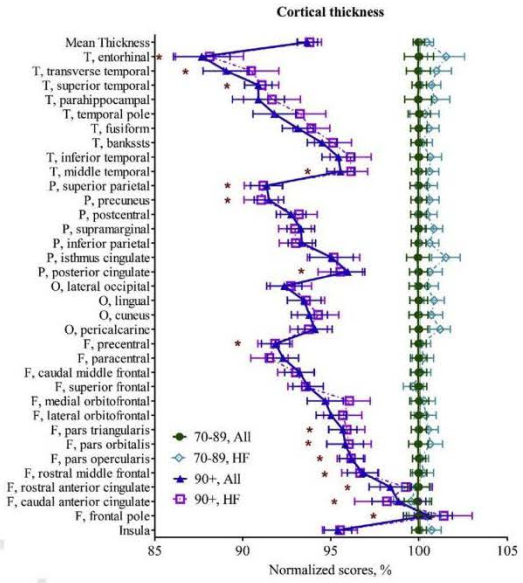

Fig. 4. Group comparison of cortical thickness between the young old (YO, 70–89 years) and oldest old (OO, 90+ years). The estimated mean and standard errors of the cortical regions of interest (ROIs) are presented in normalized values (expressed as a %) by age group and cognitive category, after controlling for sex in repeated measures ANCOVA. In the total sample, significant larger or smaller YO-OO differences ($p < 0.05$ after False Discovery Rate correction) compared to the YO–OO differences in mean cortical thickness are marked with "*". Cortical ROIs are grouped by lobe, and sorted by size of the relationships with age. Capital letters "T," "P," "O," and "F" represent temporal, parietal, occipital, and frontal lobes. Abbreviations: ANCOVA, analysis of covariance; HF, high-functioning subsample.

small vessel disease (Maniega et al., 2015; Verhaaren et al., 2013), effects of vascular risk factors such as hypertension on the volume of WMHs was nonsignificant in our sample. Accumulation of WMHs has been associated with cognitive impairment, motor dysfunction, as well as subsequent risk of mortality in the elderly in longitudinal studies (Prins et al., 2005; Sabayan et al., 2015; Silbert et al., 2008; Zheng et al., 2011). However, the mechanism and the clinical significance of such striking accumulation of WMHs in OO remains unclear; and further investigation is necessary to examine its influence on the mental and physical health at advanced age.

Another noteworthy finding in our study was the relative "preservation" of prefrontal cortex, insula, anterior cingulate, accumbens-caudate, and amygdala in the OO. Prominent involvement of the frontostriatal structures (prefrontal cortex and caudate) in aging has previously been documented by structural MRI, connectivity, and functional MRI studies (Fjell et al., 2014; Jagust, 2013; Nyberg et al., 2010), suggesting a lower level of executive function at older age (Buckner, 2004; Singer et al., 2003). Our finding is partly consistent with a few longitudinal studies of individuals aged 60–91 years, reporting decelerating decline of orbitofrontal and anterior cingulate cortices, as well as minor age effects on the inferior frontal gyri (Fjell et al., 2012; Storsve et al., 2014). Inferior frontal gyri and dorsolateral prefrontal cortex have been reported to have substantial individual differences and have been associated with longitudinal cognitive outcome (Tisserand et al., 2004). Anterior cingulate cortex is part of the frontal-subcortical neuronal circuits, and widely connected with caudate, insula, and medial orbitofrontal cortex (Jagust, 2013; Taylor et al., 2009; Tekin and Cummings, 2002). It is also a typical area where "cortical thickening" is found in cross-sectional studies, but not in longitudinal design even using participants in the same cohort study (Fjell et al., 2012; Jiang et al., 2013). Such discrepancies between cross-sectional and longitudinal designs are highly suggestive of sampling bias and cohort effect as well as survivor bias in the very old. Although still speculative, the generally "preserved" anterior part of the brain may relate to the reasons why participating individuals lived into the 10th decades of life and/or retained superior cognition. The neurobiological underpinnings of this pattern would warrant further investigation.

Taking the cerebral cortex as a whole, the overall "tempo-oposterior" pattern in this study was distinct from the previously

reported "frontal-temporal" pattern in healthy aging (Fjell et al., 2014). The age-related changes appear to be disassociated between frontal and temporal lobe, suggesting that temporal lobe is more susceptible to the aging process compared with the frontal cortex, even in those who age successfully. The nature of this study does not permit the assessment of the pathological basis of the observed pattern, or longitudinal cognitive trajectories in subjects with varying pathological insults. It is known that cerebral β-amyloidosis and neurodegeneration increase with age in cognitively healthy populations, with approximately 1 in 2 individuals showing positive amyloid imaging in their late 80's (Jack et al., 2014). Neuropathological features of AD, either alone or in combination with other pathologies such as cerebral small vessel disease, are also found to be prevalent in nondemented OO (Savva et al., 2009; Yang et al., 2013). These undetected pathologies may be present and partly account for the patterns of age effects in our sample. However, the observed pattern does not match the "temporal-predominant" or "temporal-parietal" pattern in preclinical or clinical AD (McDonald et al., 2009; Whitwell et al., 2012). A similar "temporoposterior" decline was seen in the overall nondemented group as well as the high-functioning subgroup. It is therefore likely that this is an age-related pattern not overly influenced by any particular pathology. Such a pattern could serve as the basis of understanding the mechanisms of exceptional longevity and/or cognitive maintenance at advanced age, and may shed light on dementia prevention in the elderly population.

A notable limitation of the present study is that the estimates of age-related changes are based on cross-sectional data from 2 population-based studies. Although potential cohort effects have been discussed earlier, the cross-sectional design does not taken account of individual differences in the process of aging. The present data can only address the issue of age-related differences, not aging per se. In general, longitudinal studies are more likely to detect nonlinear patterns than cross-sectional studies (Fjell et al., 2014), yet there are practical difficulties in the frail OO to assess individual variability in aging using a longitudinal design, in particular because of the high attrition seen in the very old. Our findings are therefore more likely to apply to the group that is aging "successfully." Some of the well-recognized limitations of neuroimaging studies should also be mentioned. The accuracy of the thickness estimation may vary across the cortical surface due to lower contrast-to-noise ratio in specific regions (Han et al., 2006), such as the cingulate, frontal, and temporal polar cortices. Moreover, the gray/white ratio decreases with age and the changing gray/white contrast may increase the variability of thickness estimation across cortical mantle (Salat et al., 2009b). Although the gray/white borders were defined at the location where the greatest shift in intensity occurred in the transition from GM to WM (Fischl and Dale, 2000), areas with low left-right correlations need to be interpreted with caution. Aged brains are in general prone to errors during processing. Despite our best effort in quality control, minor problems may remain undetected, possibly introducing error. These limitations, however, should not undermine the unique aspects of our study, namely a large number of OO in a cohort of elderly population, examined by high-resolution MRI and analyzed by appropriate image processing methods.

Disclosure statement

The authors have no conflicts of interests to disclose.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neurobiolaging.2016.01.006.

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Supplementary Table 3.1. Age effects on cortical thickness in men and women respectively.

ROIs	Total sample					High-functioning subsample				
	Male		Female		p-value	Male		Female		p-value
	E(70)[a]	B[b] (SE), %	E(70)[a]	B[b] (SE), %	(Age*Sex)	E(70)[a]	B[b] (SE), %	E(70)[a]	B[b] (SE), %	(Age*Sex)
Lateral occipital	**101.75**	**-3.59**	**106.35**	**-5.41**	.060	**101.44**	**-2.83**	**106.85**	**-5.63**	**.018**
Posterior cingulate[c]	**102.30**	**-2.92**	100.89	-0.55	**.019**	**103.37**	**-3.50**	100.97	-0.09	**.012**
Posterior cingulate, no outliers[c]	**101.75**	**-2.20**	101.26	-0.69	.108	**102.65**	**-2.47**	101.60	-0.33	.072
Cuneus	**101.14**	**-2.74**	**105.33**	**-4.47**	.097	**101.86**	**-2.08**	**105.47**	**-4.64**	**.037**
Temporal pole	**101.25**	**-2.26**	**105.79**	**-6.06**	**.004**	99.72	-1.33	**106.83**	**-5.65**	**.005**
Pericalcarine	**101.06**	**-1.89**	**104.12**	**-3.85**	.052	**102.37**	**-2.01**	**105.64**	**-4.59**	**.024**

The table presents those regions of interest (ROIs), which have a test-wise $p < 0.05$ for the interaction between age and sex in the cortical ROI-based analysis. Age effects on cortical thickness are examined separately in males and females, within the whole sample and the high-functioning subsample after adjusting for sex.

Abbreviations: ROIs, regions of interest; SE, standard error.

[a]Estimated value in normalised scores at 70 years old.

[b]B regression coefficient representing the relationship with age of brain measures in normalized scores per decade.

[c]Analyses were repeated in posterior cingulate, with and without 3 over-influential outliers respectively;

Bold values indicate test-wise $p < 0.05$.

3.3 Summary of main findings

In the non-demented study cohort aged 71 to 103 years, significant linear negative relationships of age with MRI-derived brain measures were seen for cortical thickness and the volumes of the cortex, subcortical grey matter and ventricles. The most prominent differences on structural MRI between the < 90 and ≥ 90 years age groups were observed in the medial temporal lobe, and parietal and occipital cortices, yielding a "temporal-posterior" pattern of brain loss in those non-demented nonagenarians and centenarians.

Prefrontal cortex, anterior cingulate, thalamus and amygdala were relatively "preserved" in the 90-plus non-demented individuals compared to the overall effects of advanced age on the brain.

Quadratic effects of age were found for white matter and WMHs. There was a positive relationship between age and WMHs, particularly the deep WMHs, which increased with advancing age.

The structural MRI profile of the subgroup of high-functioning 90-plus individuals was closely comparable to that seen in the full sample, which suggested that the patterns observed were age-related, and were not overly influenced by dementia-related ageing.

CHAPTER 4: ASSOCIATION BETWEEN STRUCTURAL BRAIN MRI AND DEMENTIA IN THE EIGHTH TO ELEVENTH DECADES OF LIFE

4.1 Overview

In the previous chapter, the structural MRI profiles of the 90-plus non-demented population were delineated. The aim of this Chapter was then to establish structural MRI markers of dementia at advanced ages. The specific aims were to:

1. Examine the association between structural brain MRI measures and dementia from 8th to 11th decades of life, and to model the odds of dementia at 80 and 95 years respectively;
2. Examine the moderating effects of age on the association between structural MRI measures and clinical dementia.

Structural MRI measures, including atrophy indices (including cortical and subcortical grey matter), WMHs and brain infarcts were examined as potential MRI markers of dementia in the 8th to 11th decades of life. The odds ratio (OR) of dementia in relation to these MRI markers, alone or in combination, was modelled at 80 and 95 years respectively; and the moderating effects of age on the dementia-MRI association were examined by testing the significance of the interaction of age by MRI measures in the logistic regression model.

4.2 Manuscript ready for submission

Association between structural brain MRI and dementia in the eighth to eleventh decades of life

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ABSTRACT

Objective: Neuropathological studies have shown that the relationship between brain pathology and dementia weakens in the very old. We sought to determine if the association between structural magnetic resonance imaging (MRI) and clinical dementia showed the same pattern.

Method: A combined sample of 318 participants (71 to 103 years), including 40 people with dementia, from the Sydney Centenarian Study and the Sydney Memory and Ageing Study were included in this cross-sectional investigation. Odds ratio of dementia in relation to MRI measures of atrophy (cortical and subcortical) and vascular injuries (white matter hyperintensities and brain infarcts) were modelled at 80 and 95 years respectively, by logistic regression, controlling for confounding factors. Moderating effects of age were examined by testing the significance of the interaction of age and the MRI measures in the model.

Results: Markers of atrophy such as cortical thickness and hippocampal volume were related to dementia at both 80 and 95 years, even though some cortical regions such as the precuneus were only significant at 80 years. Vascular markers increased the odds of dementia at 80 but not at 95. A composite MRI pathology index was much more likely to predict dementia at 80 than at 95 years.

Conclusions: The associations between dementia and markers on structural MRI are found to be attenuated at very advanced age. In particular, vascular markers are weak predictors of dementia in very old individuals. This should be taken into consideration in the assessment of dementia in nonagenarians and centenarians.

INTRODUCTION

Neuropathological studies have shown that the relationship between brain pathology and dementia weakens in the very old. Alzheimer's disease (AD) pathology, alone or in combination with vascular lesions [1, 2], has been found to be less related to dementia in those of 90-plus compared to the younger old. However, the mean interval between last cognitive assessment and brain autopsy is long, varying between 7.1 and 17 months [1, 2], during which substantial cognitive decline could have occurred. In addition, there is no widely validated protocol for scoring the diversity of vascular pathology on post-mortem examination. These limitations may affect the conclusiveness of the neuropathological studies.

Structural magnetic resonance imaging (MRI) has the advantages of being contemporaneous with the clinical evaluation and being quantitative in assessing brain vascular injuries. Yet such studies are scarce after the age 85, apart from a few post-mortem MRI investigations [3, 4]. In this study, we sought to examine markers of dementia using high-resolution structural MRI in the eighth to eleventh decades of life, and determine if the association between structural MRI and dementia weakens at older age. A combined cohort of 318 elderly, including 40 subjects with dementia, was examined; and diverse atrophy indices (cortical and subcortical) and vascular markers (white matter hyperintensities [WMHs] and brain infarcts) were investigated in relation to clinical dementia at 80 and 95 years.

MATERIALS AND METHODS

Study design

This was a cross-sectional study of age and structural MRI markers of dementia. The study was approved (HREC09382 and HC12313) by the Human Ethics Committees of

UNSW Australia and the South Eastern Sydney and Illawarra Area Health Service. All participants gave written informed consent to the study prior to the investigation.

Participants

Participants were drawn from 2 community-based longitudinal studies within the same geographic area in Sydney: the Sydney Memory and Ageing Study (MAS) [5] and Sydney Centenarian Study (SCS) [6], details of which have been published previously. Baseline cohorts of MAS and SCS were used for this study. Participants were included if they had sufficient clinical data to assess whether they had a dementia diagnosis and had completed a brain MRI on the same scanner as in the SCS (MAS n = 234, SCS n = 57). To maximise the sample size, participants who converted to dementia and/or exceeded 90 years in MAS follow-up waves (n = 59) were also included; these participants were included only once. Exclusion criteria were: 1) progressive malignancy with brain metastasis, Parkinson's disease or ongoing depression (n = 2); 2) MRI-defined brain infarcts with the longest diameter > 2 cm, as large infarcts would result in unreliable neuroimaging estimation of brain structures (n = 5); 3) problematic neuroimaging processing that could not be manually corrected (n = 25). After these exclusions, 318 individuals (MAS baseline n = 208, MAS follow-up n = 55 and SCS baseline n = 55) were included in the present study.

Assessment and diagnosis of dementia

All participants received comprehensive medical and neuropsychological assessment, followed by a depression screening, as previously described [5, 6]. The neuropsychological tests encompassed cognitive domains important for the diagnosis of dementia, i.e. premorbid intelligence, attention and processing speed, memory, language, visuo-spatial ability and executive function. Informants with regular contact were

requested to complete the Informant Questionnaire on Cognitive Decline in the Elderly [7] and the Bayer activities of daily living scale [8].

Dementia was diagnosed using the Diagnostic and Statistical Manual IV (DSM-IV) criteria, by a panel of at least three experienced specialists comprising an old age psychiatrist, a neuropsychiatrist and a neuropsychologist, based on: 1) qualitative observation from trained research psychologists in relation to participants' presentation and performance; 2) the individual's test scores on the neuropsychological battery; and 3) informant-based information about functional ability.

MRI data acquisition and processing

MRI data were acquired from Philips 3 T Achieva Quasar Dual scanner (Philips Medical Systems, Best, The Netherlands) located at Neuroscience Research Australia, Sydney with acquisition parameters for T1-weighted sequences and T2-weighted fluid attenuated inversion recovery (FLAIR) images as previously described [6].

Cortex, estimated intracranial volume (eTIV) and the cortical thickness were estimated using FreeSurfer v5.3.0 (http://surfer.nmr.mgh.harvard.edu/), based on the T1-weighted sequence imaging. Brain volumetrics were segmented and cortical surface were reconstructed in an automatic process [9, 10]. A surface map was generated based on the Desikan-Killiany Atlas and was parcellated into 34 regions of interest (ROIs) [11]. Subcortical grey matter nucleus were processed with FMRIB Software Library (FSL) using the FMRIB's Integrated Registration and Segmentation Tool [12, 13], since our previous analysis showed higher intra-class correlation between hippocampal volumes processed by FSL and manual tracing (0.67, 95% confidence interval [95%CI]: 0.54 – 0.77) compared to that between FreeSurfer and manually traced results (0.46, 95% CI: 0.28 – 0.62) in 85 individuals. Both automatic processes were visually inspected by an

individual (ZY) experienced in neuroanatomy and neuroimaging, following the ENGIMA protocols (http://enigma.ini.usc.edu/protocols/imaging-protocols/). Errors in FreeSurfer outputs were manually corrected using TKMEDIT toolbox in 110 participants. Data that failed the final step of quality control were removed from the analyses. Values from right and left hemisphere were combined, and volumes of accumbens, caudate, putamen and pallidum were combined into one variable "basal ganglia", so as to increase data reliability and to reduce the number of statistical tests.

Volumetric estimation of WMHs was based on the abnormal signal intensity on FLAIR sequences, applying a previously published method [14]. The extracted volume of WMHs was further segmented into deep and periventricular WMHs using a pre-defined rim of 7.5 – 10 mm width from the lateral ventricles. Output was visually inspected to ensure accuracy; and 6 subjects required manual correction using the FSLVIEW toolbox within FSL [12]. Five participants did have the FLAIR imaging.

Rating of MRI-defined small brain infarcts was blinded to clinical data (ZY), applying the in-house protocol for cerebral infarcts and Virchow-Robin spaces. Small brain infarcts on MRI were defined as fluid-filled cavities of between 3-20 mm in longest diameter on T1-weighted imaging, most commonly surrounded by a hyper-intensity rim on FLAIR. Forty-eight scans with ambiguous lesions were reviewed in consultation with a neuroradiologist (LD). Intra-rater test-retest reliability was excellent ($k = 0.905$), by scoring 100 scans twice, blinded to the initial rating and 1 month apart. Lacunar infarcts, cortical and cerebellar infarcts were combined in the present study, since our preliminary analyses showed similar results regardless of the location.

Statistics

Statistical analyses were carried out using SPSS (version 22.0; IBM Corp., Arkmonk, NY), with a statistical threshold for significance of $p < 0.05$ corrected for multiple comparisons by false discovery rate (FDR) [15]. Continuous brain measures were transformed into standard scores (Z scores) based on the full sample. Dichotomous MRI measures were created to define the worst 25% of cases (abnormal versus normal) within the total sample for select brain measures. Age was treated as a continuous variable in statistical analyses to maximise power, while participants were divided into 2 age groups for graphical presentations: < 88 years the young old (YO) and ≥ 88 years the oldest old (OO), with the aim of retaining similar numbers of demented subjects in each group.

Logistic regression analyses were used to examine the relationships between each of the MRI measures and dementia diagnosis, as well as the moderating effects of age on these relationships. To illustrate the effects of MRI measures on dementia diagnosis in the possible presence of moderating effects of age, model estimates of the odds ratios (ORs) of dementia were obtained separately at ages of 80 and 95 years, the 25^{th} and 75^{th} percentile age points of the demented subjects. Dependent variable for the models was clinical dementia diagnosis; independent variables were each of the brain MRI measures, continuous age and the interaction between age and the MRI measure.

To determine MRI markers that were most indicative of dementia at 80 and 95 years, multiple logistic regression analysis was used. A number of MRI-derived measures, plus their interactions with age, were initially included in the logistic regression equations, and reduced models obtained using the backward elimination procedure

(removal criterion: $p > 0.05$). Both continuous and dichotomous MRI measures were examined.

Finally, a composite MRI pathology index (hereafter "pathology index"), was created as an indicator of mixed neuropathologies; the ORs of dementia at 80 and 95 years and the moderating effect of age were examined in logistic regression.

Brain volumetrics were adjusted for eTIV in both statistical analyses and graphical presentation. All analyses were adjusted for sex. Other potential confounders such as education and APOE ε4 carriage status were examined in preliminary analyses. Inclusion of these confounders did not change the pattern of our finding, nor alter statistical significance; they were therefore not included in the models reported.

Comparison across study cohorts, and of included and excluded participants

Potential cohort effects were examined using the analysis of covariance. The MAS (baseline and follow-up cohorts) and SCS did not differ ($p > 0.05$) in the estimated means of cortical thickness and cortical and hippocampal volume, after adjusting for age, sex, education, APOE ε4 carriage status and dementia, and eTIV if a brain volumetric was the dependent variable.

Compared to nonparticipants in MAS at baseline, included MAS participants were significantly older (mean ± SD: 80.0 ± 5.7 versus 78.7 ± 4.8, $F = 14.8$, $p < 0.001$) and had more years of education (mean ± SD: 12.1 ± 3.8 versus 11.4 ± 3.4, $F = 7.57$, $p = 0.006$); but they did not differ in sex, APOE ε4 carriage status and mini-mental status examination (MMSE) scores. Compared to SCS nonparticipants, included SCS subjects were more likely to be male ($\chi^2 = 10.1$, $p = 0.002$), but they did not differ in age, level of education or APOE ε4 carriage status. Included SCS subjects had higher MMSE scores within the non-demented (mean ± SD: 27.2 ± 2.0 versus 25.6 ± 2.6, $F = 13.9$, $p <$

0.001) and dementia groups (mean ± SD: 19.3 ± 4.3 versus 15.9 ± 4.6, F = 5.0, p = 0.03), compared to nonparticipants.

RESULTS

Sample characteristics by age group and dementia status are given in Table 4.1. Demographics were comparable between different cognitive categories, except that demented YO were older and were more likely to be an APOE ε4 carrier, and demented OO had less education relative to their non-demented peers. MMSE scores were significantly lower in dementia compared to non-demented individuals.

The observed rates of dementia by age group and select dichotomous MRI measures are shown in Figure 4.1. Differences in dementia rates between the 2 MRI groups ("normal" versus "abnormal") appeared to be smaller in the OO compared to YO. "Convergence" was particularly obvious for the deep WMHs and brain infarcts.

Moderating effects of age on the MRI-dementia associations were examined by the inclusion of age by MRI measure interaction term in the logistic regressions (Table 4.2). Significant interactions with age were observed for total and deep WMHs. At 80 years of age, one standard score larger volume of deep WMHs was found to increase the odds of dementia by approximately 4-fold; whereas at 95 years, the OR was less than 2. A similar trend was noted for ≥ 2 brain infarcts (test-wise p = 0.02). Interactions with age were non-significant for the cortex or subcortical measures; nevertheless, the ORs for these markers were all smaller at 95 years than at 80 years, with one exception being the amygdala. Smaller volumes of cortex, hippocampus, amygdala and thalamus were all associated with clinical dementia at both ages; the basal ganglia were associated at 80 but not at 95 years.

As for cortical regions, the moderating effects of age were test-wise significant (test-wise $p < 0.05$) for select temporal (fusiform and transverse temporal) and parietal (isthmus cingulate, precuneus and superior parietal) cortical regions, but these were not significant after FDR correction for multiple testing (Supplementary Table 4.1, panel A). Thin cortices of the temporal and parietal lobes and select frontal areas (24 ROIs) were strong predictors of dementia at 80 years ($p < 0.05$ after FDR correction); whereas at 95, only select frontal and temporal cortical regions (supplementary table 1, panel B) were moderately related to dementia (test-wise $p < 0.05$), with none remaining significant after FDR correction.

MRI markers that were most indicative of dementia were examined by reduced logistic regression (Table 4.3). A thin cortex and small hippocampus were found to be most indicative of dementia at all ages, with no interaction effect of age (model A). When including deep WMHs and brain infarcts (≥ 2), a significant moderating effect of age was noted for the deep WMHs (model B), i.e. extensive deep WMHs were independently associated with dementia at 80, but this association weakened and was non-significant at 95. Using dichotomous MRI markers led to a similar pattern of results (model C), with significant moderating effects of age being observed for both deep WMHs and brain infarcts (≥ 2).

Finally, a pathology index was created to represent combined neuropathologies using the retained MRI markers in Table 4.3 model C: mean cortical thickness, volumes of hippocampus and deep WMHs, and ≥ 2 brain infarcts. Each of the 4 markers was scored as 0 and 1, with 1 being the worst 25% of total sample or brain infarcts ≥ 2. Pathology index was defined as the sum of these 4 scores. Rates of dementia were higher in YO compared to OO at all levels of pathology index (Figure 4.2). Note that no YO subject

(0/5) was free of dementia when having a pathology index of 3 or more; whereas 60% (9/15) of the OO with the same pathology index were non-demented ($\chi^2 = 5.45$, df = 1, p = 0.02). ORs of dementia for pathology index (Table 4.3, model D) was approximately 6-fold greater at 80 than at 95 years.

DISCUSSION

To our knowledge, this is the first study to model the effects of age and MRI markers of clinical dementia from eighth to eleventh decades of life. Using a broad range of structural MRI markers, we found that thin cortex and small hippocampus were related to dementia at both 80 and 95 years, even though some cortical regions were only significant at 80 years. Vascular markers (deep WMHs and ≥2 infarcts) increased the odds of dementia at 80, but their effects were not significant at age 95 when considered independently. A composite MRI pathology index was much more likely to predict dementia at 80 than at 95 years.

In previous studies which have generally included individuals less than 90, thin cortex [16], small hippocampus [17], extensive WMHs [18] and brain infarcts [19, 20] are established markers of dementia. This study confirms that each of the above markers is related to dementia at 80 years, even though results were somewhat inconsistent for brain infarcts (≥ 2). In addition, thinner cortex of the majority of the temporal and parietal regions was related to dementia at 80 years. This pattern overlaps with the Braak and Braak neurofibrillary pathological staging scheme [21], suggesting possible underlying AD pathology.

Few neuroimaging studies have focused on dementia after the age 85. Atrophy of the hippocampus or medial temporal lobe has been the most examined MRI marker, and is regarded as a strong indicator of mild cognitive impairment [22], dementia [3], and

longitudinal risk of incidence dementia in the very old [23]. In the Vantaa 85+ Study [24] (mean age 90) and the Sydney Older Persons Study [25] (mean age 85), WMHs were not associated with dementia or cognitive impairment. However, many of these studies used graded rather than continuous MRI measures. Their samples were relatively "young" (mean age ≤ 90). Moreover, none of these studies examined cortical measures or brain infarcts. Therefore, our investigation adds to the growing evidence that thin cortex and small hippocampus remain strong indicators of dementia in the oldest old. By contrast, neither WMHs nor brain infarcts independently contribute to clinical dementia at this age.

Our findings at 95 are supported by neuropathological studies in the very old. Pathologically defined atrophy, of the cortex and hippocampus, has been reported as a predictor of dementia from 70 to 100 years [1]. AD pathology is found to converge between dementia and non-demented subjects at advanced age [1, 2], in concordance with our results that there is no "temporal-parietal" MRI signature of dementia at 95 years. The association between symptomatic stroke/transient ischemic attack and dementia is thought to be weaker at 97 years than in younger old [26]. In another population-based neuropathological study [1], infarcts and small-vessel disease were indicative of dementia at 75 years but not at 95 years. Thus our results further support the notion that vascular lesions are common in nonagenarians and centenarians, regardless of dementia status, and their cognitive implication may be different at this age.

The composite MRI pathology index, a surrogate of combined brain pathologies, is much less indicative of dementia at 95 than at 80 years. Combined brain pathologies have been related to dementia, in both young elderly and those aged 90-plus [23, 27, 28].

Nevertheless, few studies have examined the moderating effects of age on the association between mixed neuropathologies and dementia. Only one autopsy study has taken account of the AD pathology and brain infarcts, suggesting an attenuated clinic-pathological association in nonagenarians, compared to younger old [2]. Using a broader range of MRI markers, our results provide further evidence that combined neuropathologies are, indeed, weaker predictors of dementia at more advanced ages.

Finally, it is worth noting that 60% of the oldest old with a pathology index ≥ 3 were dementia-free in our sample. These individuals demonstrated considerable brain resilience to resist dementia. Their compensatory mechanism is not immediately clear. The cortical MRI markers of dementia at 95, such as atrophy of the prefrontal cortex, may provide some insight into neuroanatomical basis of the cognitive reserve. Since the effect size was moderate in this study, a larger sample is suggested to independently replicate the findings. The underlying biology [29], behavioural and social mechanisms [30] of dementia resistance are not understood, and more research is necessary to determine factors that moderate the risk of dementia in the presence of substantial brain injury.

Several limitations of this study deserve attention. First, the sample, even though drawn from population-based studies, was not truly representative as only a small proportion of the very old agreed to undergo neuroimaging. Participants at advanced age were therefore weighted towards better physical and cognitive health. However, the potential "health" bias does not explain the attenuated MRI-dementia association at advanced age, since the differences of cognitive test scores between individuals with and without dementia are greater in the OO than in YO. Cohort effects were non-significant when tested statistically. Classification of dementia was based on standard protocol by expert

consensus. Therefore, factors other than sampling variation should be considered in the interpretation of the findings. Second, we did not have follow-up data (in SCS) to account for individual variability in cognitive trajectory and the varying speed of lesion development. It is noted that selective attrition is high at this age, and there are practical difficulties in repeating MRIs in these fragile individuals. Third, amyloid and tau imaging were not available in our study and we used atrophy indices on structural MRI to reflect the overall burden of neurodegeneration [31]. Fourth, the size of this study does not allow more detailed analyses of the interactions between different MRI markers of dementia.

In conclusion, the associations between dementia and markers on structural MRI were found to be attenuated at advanced age. In particular, vascular pathology in the brain was a weak predictor of dementia in the oldest old. These findings do not undermine the importance of promoting cardiovascular health in late life, but rather, suggest that considerable brain resilience is common in those who survive to an exceptional old age. A better understanding of the compensatory mechanisms in these non-demented subjects may shed light on dementia prevention in their younger counterparts.

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DISCLOSURE STATEMENT

The authors have no conflicts of interests to disclose.

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Table 4.1. Sample characteristics by age group and dementia status.

Characteristic	71 – 87 years		88 – 103 years	
	No dementia (n = 202)	Dementia (n = 22)	No dementia (n = 76)	Dementia (n = 18)
Age, years	**78.4 (4.2)**	**82.4 (4.3)**	95.0 (3.7)	95.0 (4.7)
Female sex	106 (52.4)	9 (40.9)	38 (50.0)	13 (72.2)
Education, years	12.2 (3.5)	12.9 (4.9)	**11.2 (3.8)**	**9.0 (2.6)**
MMSE[a]	**28.2 (1.4)**	**23.5 (3.4)**	**27.2 (1.9)**	**20.8 (4.1)**
APOE ε4 carriage[b]	**49 (24.6)**	**10 (45.5)**	10 (13.7)	2 (13.3)

[a] MMSE scores were prorated from raw scores; all participants completed more than 27/30 of the MMSE scoring items.

[b] Excludes 10 participants without APOE genotype data.

Abbreviation: MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination.

Data are mean (standard deviation) or n (%).

Bold values indicate significant difference ($p < 0.05$ of ANOVA or Fisher's exact test) in mean or portion between the demented and non-demented participants within the same age group.

Table 4.2. Odds ratio (ORs) of dementia in relation to brain MRI measures, modelled at the ages of 80 and 95 years.

	N	At 80 years OR (95% CI)	At 95 years OR (95% CI)	Wald[a] (age*MRI)	p-value[a] (age*MRI)
Measures of cortex					
Cortex	314	**9.02 (3.77 – 21.57)**	**8.13 (3.20 – 20.61)**	0.07	0.79
Mean cortical thickness	318	**4.08 (2.17 – 7.66)**	**2.35 (1.30 – 4.24)**	2.09	0.15
Subcortical nuclei					
Hippocampus	309	**5.48 (2.83 – 10.60)**	**3.23 (1.60 – 6.51)**	1.41	0.24
Amygdala	273	**1.68 (1.06 – 2.66)**	**2.71 (1.26 – 5.84)**	1.43	0.23
Thalamus	309	**3.52 (1.88 – 6.60)**	**2.81 (1.49 – 5.30)**	0.36	0.55
Basal ganglia	238	**3.01 (1.53 – 5.89)**	*2.28 (0.96 – 5.39)*	0.33	0.57
Vascular markers					
Total WMHs volume	313	**3.22 (1.93 - 5.37)**	*1.49 (1.03 - 2.16)*	6.95	**<0.01**
Deep WMHs	313	**4.00 (2.26 - 7.11)**	**1.52 (1.06 - 2.19)**	9.28	**<0.01**
Periventricular WMHs	313	1.54 (1.03 - 2.32)	1.25 (0.79 - 1.98)	0.57	0.45
No. of infarcts				6.69	0.04
0 infarct	242	1.00 (reference)	1.00 (reference)		
1 infarct	46	2.27 (0.67 - 7.66)	0.61 (0.19 - 2.02)	2.67	0.10
2 or more infarcts	26	**6.66 (1.82 - 24.46)**	*1.00 (0.29 - 3.46)*	5.37	*0.02*

ORs were generated from a series of logistic regression models; the outcome for each model was dementia status and the independent variables were one MRI marker, age and the interaction between age and the MRI marker, as well as sex, and estimated intracranial volume if a brain volumetric was the independent variable.

[a] Wald and p-value represent test-wise value of the effect of age on the association between MRI measures and dementia in the model.

Abbreviation: 95% CI, 95% confidence interval; MRI, magnetic resonance imaging; OR, odds ratio; WMHs, white matter hyperintensities.

Bold values indicate $p < 0.05$ after correction for multiple testing by False Discovery Rate (FDR); *italic* values indicate the p-value < 0.1 after FDR correction.

Table 4.3. Most indicative markers of dementia at 80 and 95 years.

	At 80 years OR (95% CI)	At 95 years OR (95% CI)	Wald [a] (age*MRI)	p-value [a] (age*MRI)
Model A, neurodegenerations, Nagelkerke R^2 = 0.37				
Mean cortical thickness	**2.75 (1.62 – 4.66)**		-	-
Hippocampus	**3.93 (2.30 – 6.72)**		-	-
Model B, neurodegenerations and vascular pathology, Nagelkerke R^2 = 0.47				
Mean cortical thickness	**3.12 (1.75 – 5.56)**		-	-
Hippocampus	**3.70 (2.05 – 6.66)**		-	-
Deep WMHs	**4.21 (2.12 – 8.35)**	*1.45 (0.96 – 2.20)*	8.53	**0.03**
Model C, dichotomous variables of neurodegenerations and vascular pathology, Nagelkerke R^2 = 0.42				
Mean cortical thickness	**6.78 (2.64 – 17.42)**		-	-
Hippocampus	**6.59 (2.46 – 17.65)**		-	-
Deep WMHs	**13.38 (4.26 – 42.09)**	1.47 (0.48 – 4.57)	8.54	**<0.01**
≥2 Infarcts	**5.64 (1.04 – 30.49)**	0.61 (0.14 – 2.69)	4.49	**0.04**
Model D, pathology index ranging from 0 to 4, Nagelkerke R2 = 0.42				
Pathology index	**12.86 (5.43 – 30.48)**	**2.18 (1.33 – 3.58)**	15.03	**<0.01**

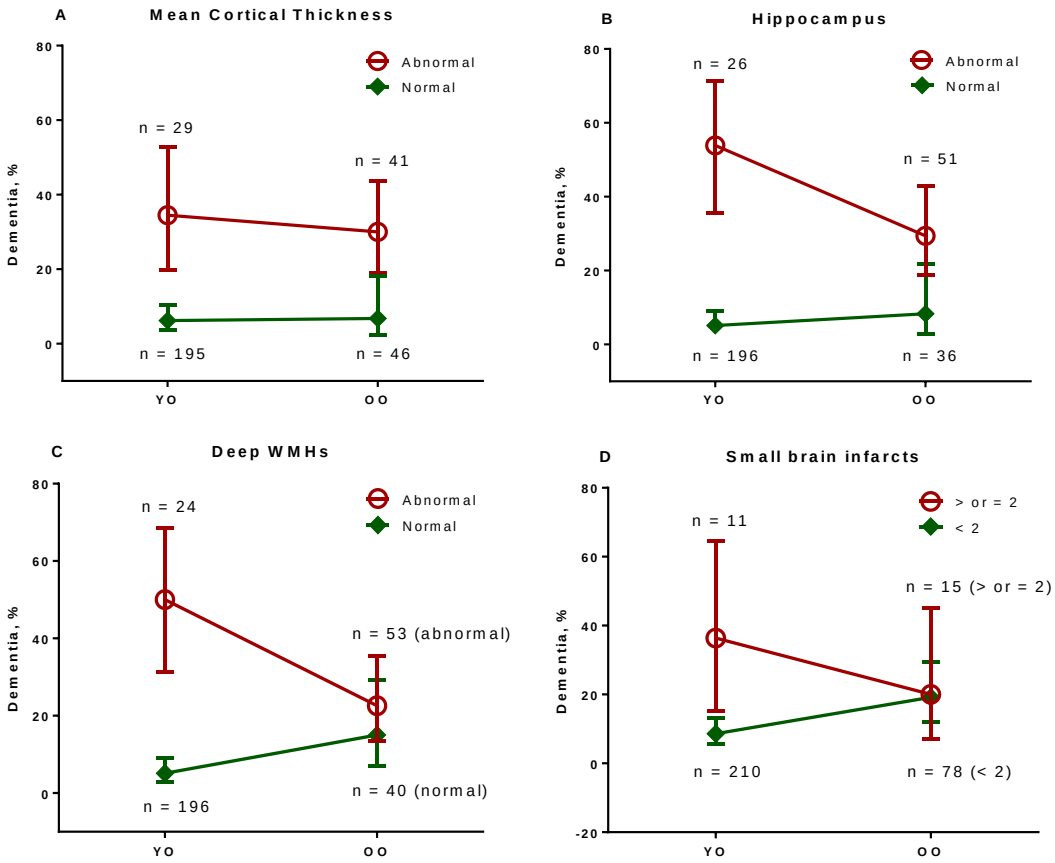
Reduced logistic regression models were obtained using backward elimination. Odds ratios (ORs) were generated from 4 multivariate logistic regression models with the outcome being dementia status. All models were adjusted for sex, models A and B were also adjusted for estimated intracranial volume.

[a] Wald and p-value represent the significance of age effect on the association between MRI measures and dementia.

Abbreviation: CI, confidence interval; MRI, magnetic resonance imaging; OR, odds ratio; WMHs, white matter hyperintensities.

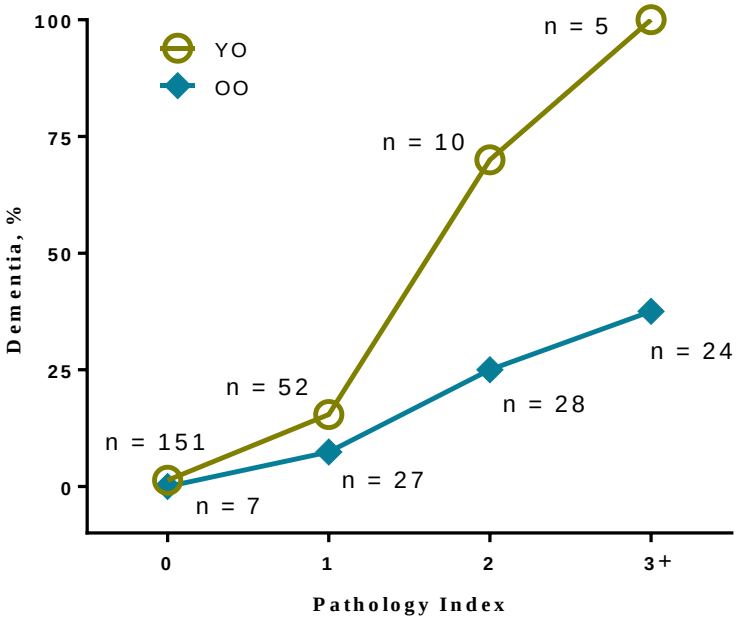
Bold values indicate $p < 0.05$; *italic* values indicate the p-value < 0.1.

Model A initially included the mean thickness, volumes of cortex, hippocampus, amygdala and thalamus, and their interaction with age before backward elimination. Brain measures are transformed in standard scores. Model B initially included the mean thickness, volume of hippocampus, deep WMHs, brain infarcts (≥ 2 or < 2) plus their interactions with age. Continuous brain measures are transformed in standard scores. Model C included dichotomised mean thickness, hippocampus, deep WMHs and brain infarcts (≥ 2 or < 2) and their interaction with age. Model D included pathology index and its interaction with age.



Participants were divided into < 88 and ≥ 88 years, the young old (YO) and oldest old (OO). "Abnormal" MRI measures were defined as the worst 25% of cases within the total sample, while the rest defined as "normal". Percentages of participants with dementia were obtained for "abnormal" and "normal" MRI measures groups, and separately for YO and OO individuals. Error bars represent the estimated 95% confidence interval of the observed rates.

Figure 4.1. Observed rates of dementia by age group and dichotomous MRI measures.



Participants were divided into < 88 (young old, YO) and ≥ 88 years (oldest old, OO). Pathology index was generated from 4 dichotomous variables (mean cortical thickness, hippocampal volume, deep white matter hyperintensities and brain infarcts), ranging from 0 to 4.

Figure 4.2. Rates of dementia by age group and pathology index.

Supplementary Table 4.1. Odds ratio (ORs) of dementia in relation to brain cortical regions of interest (ROIs), modelled at the ages of 80 and 95 years.

Cortical ROIs[b]	N	At 80 years OR(95% CI)	At 95 years OR(95% CI)	Wald[a] (Age*MRI)	p[a] (Age*MRI)
Panel A, ROIs with test-wise significant effects of age					
P, isthmus cingulate	318	**2.11 (1.22 - 3.64)**	1.01 (0.62 - 1.63)	4.68	0.03
P, precuneus	315	**3.23 (1.83 - 5.69)**	1.49 (0.82 - 2.71)	4.33	0.04
P, superior parietal	318	**2.81 (1.54 - 5.10)**	1.32 (0.82 - 2.13)	4.83	0.03
T, fusiform	316	**3.61 (1.97 - 6.59)**	1.6 (0.95 - 2.68)	4.67	0.03
T, transverse temporal	318	**2.42 (1.40 - 4.19)**	1.15 (0.69 - 1.89)	4.29	0.04
Panel B, ROIs with test-wise significant (test-wise p < 0.05) OR at 95 years					
F, lateral orbitofrontal	315	**2.07 (1.16 - 3.7)**	1.59 (1.06 - 2.39)	0.72	0.40
F, pars opercularis	316	**2.07 (1.21 - 3.52)**	*1.81 (1.18 - 2.76)*	0.19	0.67
F, pars orbitalis	315	**2.17 (1.22 - 3.87)**	*2.04 (1.19 - 3.49)*	0.03	0.87
F, pars triangularis	316	1.50 (0.90 - 2.52)	1.57 (1.03 - 2.39)	0.02	0.89
F, rostral middle frontal	315	**1.76 (1.09 - 2.84)**	1.72 (1.06 - 2.78)	0.01	0.94
T, entorhinal	316	**4.27 (2.39 - 7.63)**	*2.58 (1.43 - 4.66)*	1.63	0.20
T, parahippocampal	318	**2.47 (1.38 - 4.41)**	1.82 (1.08 - 3.08)	0.62	0.43
T, superior temporal	318	**3.42 (1.85 - 6.35)**	*2.39 (1.24 - 4.59)*	0.78	0.38
T, middle temporal	314	**2.42 (1.43 - 4.09)**	1.88 (1.04 - 3.41)	0.44	0.51
T, banks of superior temporal sulcus	318	**3.12 (1.79 - 5.45)**	1.94 (1.11 - 3.38)	1.67	0.20
P, inferior parietal	317	**3.03 (1.72 - 5.35)**	1.78 (1.03 - 3.09)	2.15	0.14
P, supramarginal	317	**2.81 (1.66 - 4.76)**	1.97 (1.16 - 3.37)	1.14	0.29
Panel C, remaining ROIs					
F, caudal anterior cingulate	316	1.28 (0.79 - 2.10)	1.36 (0.92 - 2.02)	0.04	0.84
F, caudal middle frontal	317	**2.40 (1.44 - 4.00)**	1.36 (0.82 - 2.24)	2.96	0.09
F, medial orbitofrontal	315	**2.67 (1.39 - 5.09)**	1.41 (0.91 - 2.18)	3.10	0.08
F, paracentral	317	1.40 (0.85 - 2.30)	0.77 (0.49 - 1.21)	3.73	0.05
F, precentral	317	**2.28 (1.35 - 3.85)**	1.50 (0.83 - 2.72)	1.41	0.24
F, rostral anterior cingulate	312	1.04 (0.64 - 1.7)	1.09 (0.76 - 1.57)	0.03	0.86
F, superior frontal	315	**2.15 (1.26 - 3.67)**	1.44 (0.84 - 2.48)	1.30	0.26
F, frontal pole	313	1.43 (0.87 - 2.34)	1.26 (0.83 - 1.90)	0.18	0.67
T, inferior temporal	312	**2.11 (1.24 - 3.58)**	1.63 (0.96 - 2.75)	0.55	0.46
T, temporal pole	314	**2.31 (1.26 - 4.23)**	1.25 (0.89 - 1.77)	3.53	0.06
P, postcentral	317	**2.43 (1.36 - 4.33)**	1.50 (0.89 - 2.53)	1.90	0.17
P, posterior cingulate	318	*1.55 (0.97 - 2.48)*	1.13 (0.77 - 1.65)	1.26	0.26
O, cuneus	318	1.31 (0.79 - 2.17)	0.84 (0.53 - 1.33)	2.00	0.16

(Supplementary table 4.1. Continued)					
O, lateral occipital	316	**2.83 (1.54 - 5.21)**	1.36 (0.77 - 2.40)	3.67	0.06
O, lingual	318	*1.68 (1.01 - 2.81)*	1.49 (0.84 - 2.64)	0.13	0.72
O, pericalcarine	318	1.06 (0.67 - 1.67)	0.87 (0.55 - 1.37)	0.45	0.50
Insula	315	1.60 (0.93 - 2.76)	1.37 (0.94 - 2.01)	0.27	0.60

ORs were generated from a series of logistic regression models; the outcome for each model was dementia status and the independent variables were one cortical ROI, age and the interaction between age and the MRI marker and sex.

[a] Wald and p-value represent test-wise value of the effect of age on the association between MRI measures and dementia in the model.

[b] Capital letters "F", "T", "P" and "O" refer to frontal, temporal, parietal and occipital lobes respectively.

Abbreviation: 95% CI, 95% confidence interval; MRI, magnetic resonance imaging; OR, odds ratio; WMHs, white matter hyperintensities.

Bold values indicate $p < 0.05$ after correction for multiple testing by False Discovery Rate (FDR); *italic* values indicate the p-value < 0.1 after FDR correction.

4.3 Summary of main findings

Among a broad range of structural MRI markers, thin cortex and small hippocampus were found to be strong indicators of dementia at both 80 and 95 years, even though some cortical regions, such as precuneus and isthmus cingulate, were only significant at 80 years. By contrast, vascular markers (deep WMHs and ≥2 infarcts) increased the odds of dementia at 80, but not independently at 95 years.

A composite MRI pathology index was associated with dementia at both 80 and 95 years. Nevertheless, it was much more likely to predict dementia at 80 than at 95 years, suggesting an overall attenuated MRI-dementia association at advanced age.

Select prefrontal and temporal cortices and subcortical nuclei were moderately (test-wise $p < 0.05$) associated with clinical dementia at 95 years, which might provide insight into the possible mechanisms of brain resilience in exceptional longevity.

CHAPTER 5: STRUCTURAL MRI BIOMARKERS OF MILD COGNITIVE IMPAIRMENT FROM YOUNG ELDERS TO CENTENARIANS

5.1 Overview

The previous chapter examined structural MRI markers of dementia in the 8th to 11th decades of life. Further, this study was to investigate if brain MRI could distinguish dementia in its prodromal stage, mild cognitive impairment (MCI), from cognitively normal individuals. The aims of Chapter 5 were:

1. To examine structural brain MRI markers of amnestic MCI (aMCI) and non-amnestic MCI (naMCI) from 71 to 103 years;
2. To determined brain structures on MRI that best distinguished aMCI from cognitively normal individuals in the young old (<85) and oldest old (85-plus) groups respectively.

Participants who were diagnosed with aMCI, or naMCI or normal cognition were included. Brain volumetrics of cortical and subcortical grey matters, as well as WMHs, were included as potential MRI markers of different MCI subtypes. The mean differences between cognitive categories on structural MRI were estimated using general linear models, while the best indicators of aMCI in the young old and oldest were examined by reduced logistic regression models.

5.2 Publication: *Curr Alzheimers Res.* 2016; 13(3): 256 -267

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FINAL

Structural MRI Biomarkers of Mild Cognitive Impairment from Young Elders to Centenarians

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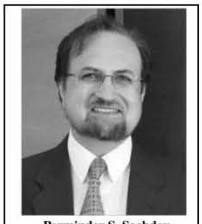

Perminder S. Sachdev

Abstract: Underpinnings of mild cognitive impairment (MCI) change with increasing age. We hypothesize that MRI signatures of mild cognitive impairment (MCI) would be different at a higher age compared to younger elders. Methods – 244 participants (71-103 years) from the Sydney Memory and Ageing Study and the Sydney Centenarian Study were categorized as amnestic MCI (aMCI), non-amnestic MCI (naMCI) or cognitively normal (CN). Brain "atrophy" and white matter hyper-intensities (WMHs) associated with MCI subtypes and age effects were examined by general linear models, controlling for confounding factors. Reduced logistic regressions were performed to determine structures that best discriminated aMCI from CN in individuals <85 and those ≥85 years. Results – aMCI was associated with smaller volumes of overall cortex, medial temporal structures, anterior corpus callosum, and select frontal and parietal regions compared to CN; such associations did not significantly change with age. Structures that best discriminated aMCI from CN differed however in the <85 and ≥85 age groups: cortex, putamen, parahippocampal, precuneus and superior frontal cortices in <85 years, and the hippocampus, pars triangularis and temporal pole in ≥85 years. Differences between naMCI and CN were small and non-significant in the sample. WMHs were not significantly associated with MCI subtypes. Conclusions – Structural MRI distinguishes aMCI, but not naMCI, from CN in elderly individuals. The structures that best distinguish aMCI from CN differ in those <85 from those ≥85, suggesting different neuropathological underpinnings of cognitive impairment in the very old.

Keywords: Advanced age, Alzheimer's disease, aMCI, brain atrophy, naMCI, structural MRI.

1. INTRODUCTION

Structural brain magnetic resonance imaging (MRI) has been widely used as a non-invasive method to assist the diagnosis of mild cognitive impairment (MCI), which is often a precursor to dementia [1-3]. Amnestic MCI (aMCI) is of particular interest since it is considered to be the prodromal phase of Alzheimer's disease (AD) [4]. Relative to cognitively normal (CN) subjects, a pattern of atrophy spreading from mesial temporal lobe to temporo-parietal cortices in aMCI individuals has been well established [1, 3, 5-8]. Such pattern is consistent with the current hypothesis of AD pathogenesis [2], thus is implicated in differential diagnosis and/or monitoring of disease progression. In contrast, non-amnestic MCI (naMCI) is thought to have heterogeneous patterns of brain atrophy depending on different underlying disorders [7, 9]. However, the understanding of MRI signatures of MCI are based on elders of relatively young age (mean approximately 75 years); and they may not be applied at advanced age, i.e. 85 years and over.

From a neuropathological standpoint, underpinnings of cognitive impairment changes with increasing age. Although AD neuropathology remains the leading neurodegeneration in people over the age of 85 years, other aging-related brain pathologies also become prevalent [10]. While the correlation between pathological features of AD and dementia has been found to be reduced at advanced age [11], contribution of other pathologies, such as hippocampal sclerosis, small vessel disease and the 43-kDa transactive response sequence DNA-binding protein, is increasingly recognized [12-15]. Despite these established dementia correlates, none of them could clearly distinguish cognitive impairment from normal subjects before clinical dementia is evident in the 90+ age group [13], indicating limitations of using single pathology in explaining early cognitive dysfunction in the very old.

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As a reflection of the overall burden of brain pathologies, structural MRI might serve as a better approach to distinguish MCI from CN subjects at advanced age. Such studies are scarce, apart from a few postmortem MRI reports in ≥85 years [15, 16] and one recent study in 183 participants aged 72-96 years [17], suggesting hippocampal volume and white matter lesions could be discriminative of MCI from normal. However, not the entire brain areas were explored in those ≥85 years; it is also unknown whether the MRI signatures of cognitive impairment would be related to age.

In this cross-sectional MRI study, both volumetric measures of cortical and subcortical regions of interest (ROIs) were examined, the white matter hyper-intensities (WMHs) were used as surrogates of small vessel disease. We aim to explore structural MRI biomarkers that could distinguish aMCI or naMCI from normal in an elderly population aged 71 to 103 years, and hypothesize that MRI signatures of cognitive impairment would be different at advanced age (≥ 85 years) compared to their younger counterparts (<85 years).

2. MATERIALS AND METHOD

2.1. Study Sample

Two hundred and forty-four non-demented community dwelling individuals, aged from 71 to 103 years (mean age 83.2 years, female 52.4%) comprised the sample. Participants were drawn from two community-based longitudinal studies: Sydney Centenarian Study (SCS) and Sydney Memory and Ageing Study (MAS), details of which have been previously reported [18, 19]. Fig. (**1**) summarizes the recruitment and selection process for the study. Participants aged 71-89 years (n=234) were participants of MAS at baseline; and those aged 90-94 years (n=32) were recruited from follow-up waves of MAS [18]; no participant was included twice. Individuals aged 95 years and above (n=57) were recruited from SCS [19]. Exclusionary criteria for the current study were presence of brain infarct >2 cm in diameter on MRI (n=5), diagnosis of dementia (n=14), unclassifiable cognitive status (n=29), other diagnosed CNS disease (Parkinson's disease, epilepsy, psychotic disorders including ongoing depression) or progressive malignancy (n=2) and unsatisfactory neuroimaging quality (n=36). Both MAS (approval no. HREC09382) and SCS (approval no. HC12313) were approved by the Human Ethics Committees of the University of New South Wales and the South Eastern Sydney and Illawarra Area Health Service. All participants gave written informed consent to participate in the study.

2.2. Categorization of Cognitive Status

Participants of SCS and MAS were assigned to one of three cognitive categories: cognitively normal (CN), MCI and dementia (the last for exclusion purposes). Such categorization was made by an expert panel comprising at least three experienced clinicians from a panel of neuropsychiatrists, geriatric psychiatrists, a clinical neuropsychologist and a clinical psychologist, and based on: 1) detailed description from trained research psychologists, in particular any factors such as sensory impairment, motor constraint or limited English language that might have affected neuropsychological performance; 2) qualitative reports from the informants of regular contact, plus quantitative informant questionnaires including the short form of the Informant Questionnaire on Cognitive Decline in the Elderly (Short IQ CODE) [20] and the Bayer activities of daily living scale (BADLs) [21]; 3) neuropsychological battery encompassing cognitive domains important for the diagnosis of dementia including premorbid intelligence, attention/processing speed, memory, language, visuo-spatial ability and executive function, details of which had been published previously [18, 19]. A proportion of SCS participants (n=22) only completed the Addenbrooke's Cognitive Examination Revised (ACE-R) [22] as they could not tolerate a more detailed assessment.

MCI was diagnosed according to the International Consensus Criteria and further categorized into amnestic (aMCI) and non-amnestic (naMCI) subtypes [23]. Single- and multiple-domain MCI were pooled together. Individuals with intact neuropsychological performance across all tested cogni-

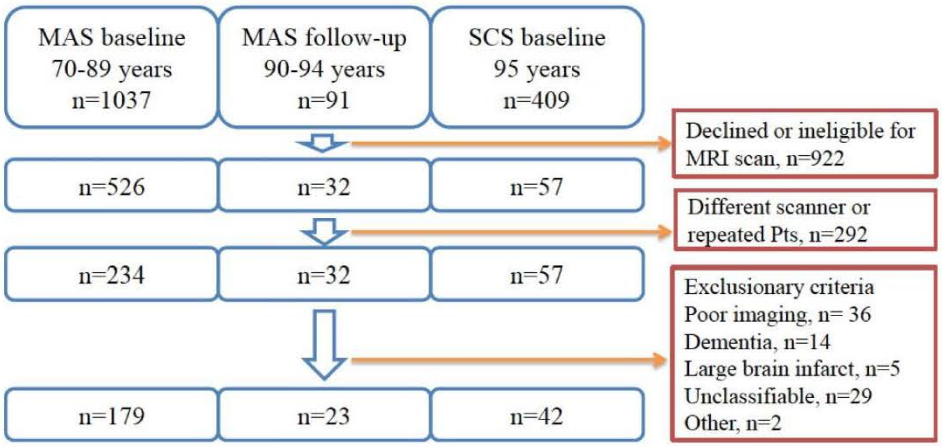

Fig. (1). Summary of the recruitment and selection process of the study. The study sample was pooled from the Sydney Centenarian Study (SCS) and Sydney Memory and Ageing Study (MAS).

tive domains and a preserved level of functioning on daily living were categorized as CN. Unclassifiable cases due to limited English language, severe sensory impairment, or too many missing data on neuropsychological tests or informant's report were excluded from the study. Diagnosis of dementia (for exclusion purposes) was based on Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria [24]. While age- and education-stratified normative data under the age of 90 years are widely available, normative data from the 90+ Study [25] were employed for the Trail Making Test [26], Boston Naming Test [27], letter fluency [28], animal fluency [28] and Mini Mental State Examination (MMSE) [29] in participants of 90+ years; performance on the remainder of the tests was judged against the next oldest available normative values. In order to categorize participants who only completed ACE-R, an individual's performance was compared against the mean and standard deviation of the normal functioning SCS participants (within the same age range) who had completed the full neuropsychological battery.

2.3. MRI Acquisition and Data Processing

All imaging was performed with the same scanner, Philips 3 T Achieva Quasar Dual scanner (Philips Medical Systems, Best, The Netherlands) located at Neuroscience Research Australia (NeuRA), Sydney. T1-weighted 3D images were acquired using the following acquisition parameters: TR = 6.39 ms, TE = 2.9 ms, flip angle = 8°, matrix size = 256 × 256, FOV = 256 × 256 × 190, and slice thickness = 1 mm with no gap in between, yielding 1 × 1 × 1 mm^3 isotropic voxels. T2-weighted fluid attenuated inversion recovery (FLAIR) sequence was acquired in coronal orientation with TR = 10000 ms, TE = 110 ms, inversion time TI = 2800 ms; matrix size = 512 × 512; slice thickness = 3.5 mm with no gap between slices, yielding spatial resolution of 0.488 × 0.488 × 3.5 mm^3 per voxel.

T1-weighted 3D images were processed with FreeSurfer v5.3.0 (http://surfer.nmr.mgh.harvard.edu/) at the Neuroimaging Laboratory, Centre for Healthy Brain Ageing (CHeBA), UNSW Medicine. Scans were segmented to yield data for cortical and subcortical volumetric regions of interest (ROIs), as previously described [30; 31]. We combined values of both hemispheres to reduce the number of statistical tests and increase the estimation reliability. Corpus callosum (CC) was divided into anterior (rostrum, genu, rostral body and mid-body) and posterior (isthmus and splenium) parts, since our preliminary analysis on its sub-regions had shown distinct results. The cortical surface was reconstructed and parcellated into 34 cortical ROIs using an automatic approach [30, 31] and the "Desikan-Killiany" cortical atlas [32] as previously reported. Estimated total intracranial volume (eTIV) was generated using an atlas scaling and covariance approach as previously published [33]. The automated MRI processing was reviewed for quality. Common errors, often caused by failed intensity normalization, wrongly segmented subcortical white matter hyper-intensities or inclusion of dura or vessel to the cortex, were manually corrected by the same trained operator (ZY) using TKMEDIT toolbox in FreeSurfer on 52.9% of the participants of our initial sample. The quality of MRI output after manual editing was then classified into "pass"– all regions usable, "partial" – more than 30 of the 34 cortical ROIs usable, and "fail"– excluded from our sample pool.

Volumes of subcortical ROIs were generated using FMRIB's Integrated Registration and Segmentation Tool (FIRST) [34]. Values beyond 1.96 standard deviation (SD) were visually inspected applying the ENIGMA protocols (http://enigma.ini.usc.edu/protocols/imaging-protocols/) to ensure accuracy. We combined the volume of caudate and accumbens into one ROI as "accumbens-caudate" to achieve better accuracy due to indistinct boundaries between these 2 structures in a considerable proportion of cases. Values of subcortical ROIs were excluded if they failed visual quality inspection, and missing values were mostly for the basal ganglia and the amygdala.

Volumetric estimation of white matter hyper-intensities (WMHs) was performed using our in-house method as previously published [35]. Both the T1-weighted and FLAIR images were used, and WMHs were detected and segmented into volumes of periventricular and deep WMHs respectively, using an automated procedure. Accuracy of the WMHs processing was visually inspected, and unsatisfactory segmentations were manually corrected using the FSLVIEW toolbox within the FMRIB Software library (FSL) v5.0.1 [36]. Seven Participants in MAS did not have T2-weighted FLAIR images.

2.4. Statistical Analysis

Surface-based analyses on cortical volume were performed at each vertex using general linear model by FreeSurfer (www.surfer.nmr.mgh.harvard.edu), with cognitive categories as the contrast, corrected for age, sex and eTIV. Only participants with a "pass" imaging quality (n=237) were used. MCI-associated atrophy as well as its statistical significance across the cortical mantle were projected on to a semi-inflated template brain using a circularly symmetric Gaussian kernel with a full width at half maximum (FWHM) at 20 mm. The statistical significance was re-thresholded by false discovery rate (FDR) <0.05 [37].

ROI-based analyses on all volumetric measures were carried out by SPSS 21.0 (SPSS, Chicago, IL), applying general linear models and binary logistic regressions. We firstly presumed consistent distinctions between MCI (aMCI or naMCI) and CN at any age within our sample, and used general linear models to examine the mean differences controlling for age, sex and eTIV. Further, an interaction term of age and cognitive category was introduced into the model in order to explore any converging or diverging distinction between cognitive groups that may occur in the process of advanced aging. Lastly, we focused on the aMCI subgroup and divided it into 2 age groups: <85 and ≥85 years. The cut-off point of 85 years was created with the goals of keeping similar age span and retaining relatively equal numbers of aMCI subjects in each subgroup. Reduced logistic regression analyses were performed in order to identify structures that best discriminated aMCI from CN in the 2 age groups. To arrive at the best discriminators, odds ratios (ORs) for each brain ROI were examined individually; and the top 5 ROIs with the smallest p-values were included to fit the base model of logistic regression using cortical ROIs or the remains of volumetric measurements respectively. Strategies

of backward elimination were then applied and ROIs with $p<0.10$ were kept in the final model, controlling for age, sex and eTIV. Interactions between the 2 age groups and the best discriminators of cognition were also examined with logistic regression. Logistic regression was not performed on naMCI participants due to inadequate sample size (≥85 years, n=6). Volumes of WMHs were Ln transformed to more closely approximate the normal distribution (skewness <1 after transformation). All the volumetric measurements were then transformed into Z scores (standard scores) within each ROI across the entire study population [38]. Statistical significance was defined as an α-level of $p<0.05$ after correction for multiple testing by FDR [39]. Other potential confounders that were initially examined in the analysis included education, APOE ε4 carriage status and the presence of medical comorbidities (stroke, transient ischemic attack, coronary artery disease, hypertension, high cholesterol, diabetes mellitus, smoking and depression). Repeating the general linear analysis after the inclusion of each of these potential confounders did not change the patterns of our finding, thus these variables were not included in the model reported.

3. RESULTS

Characteristics of the study sample by cognitive categories are presented in Table **1**. Cognitive groups did not differ in sex or education, but did differ significantly in mean age of the ≥85 years subgroup, APOE ε4 carrier proportion of the <85 years subgroup and the MMSE scores in both age groups.

Demographics and medical history of the included participants from SCS and MAS were generally comparable with base sample of the 2 studies, as shown in supplementary Table **1**. Some variations were observed. The included SCS participants had significantly smaller proportion of women (45.2% vs 72.4%, χ^2=12.936, p=0.001) and higher MMSE scores (mean ± SD: 27.2 ± 2.1 vs 21.7 ± 5.9, F=42.270, $p<0.001$) relative to the remaining ones. Such discrepancies are most likely related to dementia, in particular demented women, being excluded from the current study. Included MAS participants had significantly higher age (mean ± SD: 80.1 ± 5.8 versus 78.7 ± 4.8 years, F=12.739, $p<0.001$) and more years of education (mean ± SD: 12.1 ± 3.8 versus 11.5 ± 3.4, F=6.259, p=0.013) compared to the rest of MAS subjects at baseline. This is to be expected as a proportion of the MAS participants was from later waves.

3.1. MCI-Related Brain Atrophy in Full Sample

Estimated mean differences of those test-wise significant ($p<0.05$) brain ROIs between CN and MCI subtypes are shown in Table **2**; results of all ROIs are presented in supplementary Table **2**. aMCI was associated with significantly (FDR<0.05) smaller volumes in the overall cortex, hippocampus and anterior CC as well as select cortical regions, including the cingulate isthmus, parahippocampal gyrus, pars orbitalis, pars triangularis, precuneus, and superior temporal and the frontal polar cortices. Test-wise significant differences ($p<0.05$) between naMCI and CN participants were seen in the thalamus, entorhinal and pericalcarine cortices, but none of these ROIs remained significant after correction for multiple testing (FDR>0.05). There was no significant difference ($p>0.05$) in the volume of periventricular or deep WMHs between MCI (either aMCI or naMCI) and normal participants.

Surface-based analyses of neocortical "atrophy" associated with MCI subtypes provided a comprehensive view across the cortical mantle as shown in Fig. (**2**). Similar to ROI-based analysis, smaller cortical volume in the aMCI subjects was seen primarily on medial and lateral temporal, orbitofrontal, cingulate isthmus, precuneus and paracentral cortices of both hemispheres, with slightly more reduced volume on the right (FDR<0.05). The anterior part of inferior frontal gyrus and medial side of superior frontal gyrus on the right were also smaller in the aMCI (FDR<0.05). The pattern of cortical differences in naMCI relative to normal controls was characterized by significantly smaller volume in entorhinal cortex (FDR<0.05) but also greater volume in small areas of superior frontal gyrus (FDR<0.05).

3.2. Effects of Age on MCI-Related Brain Atrophy

Test-wise significant age effects on MCI-associated brain atrophy are illustrated in Fig. (**3**). For the effect on "atrophy" in the temporal pole, a significant age by aMCI interaction was found (p=0.016). From Fig. (**3A**), this can be seen to represent a larger difference in levels of atrophy between aMCI and CN participants at older age. Test-wise significant interactions between age and naMCI were observed for effects on "atrophy" in the posterior CC (p=0.035) and medial orbital frontal cortex (p=0.022), which can be seen to indicate greater effects of naMCI (versus CN) on atrophy levels in the higher age ranges (Fig. **3B** and **3C**). All of the above interactions however became non-significant after FDR correction for multiple testing. There were no test-wise statistically significant interactions between age and diagnostic categories for any of the other ROIs.

3.3. Discriminators of aMCI from CN in Young and Old Subgroups

The ORs of the selected ROIs for reduced logistic regression in predicting aMCI status in <85 and ≥85 years are shown in Table **3**; ORs of all the ROIs in the logistic regression were listed in supplementary Table **3**. Discriminators of aMCI from CN individuals in the reduced logistic regression model are presented in Table **4**. In the <85 group, the cortex and putamen were retained in the final model and regarded as best discriminators of aMCI from CN among the overall & subcortical ROIs, yielding an OR of 0.418 (95% confidence interval, 95% CI: 0.152–1.150) and 0.592 (95% CI: 0.330–1.072) respectively per one standardized score increase in volume, adjusted for age, sex and eTIV. Discriminators among the cortical ROIs in <85 years included the parahippocampal, precuneus and superior frontal cortices, estimated to have an OR of 0.488 (95% CI: 0.272–0.874), 0.546 (95% CI: 0.285–1.046) and 0.427 (95% CI: 0.203–0.897) respectively. In the ≥85 years however, only the hippocampus from the overall & subcortical ROIs was a discriminator of cognitive status, with OR estimated to be 0.477 (95% CI: 0.226–1.006) per one standardized score increase in volume. Cortical ROIs that best discriminated aMCI from CN in participants of ≥85 years included the pars

Table 1. Demographics of participants in different cognitive categories.

	Normal	aMCI	naMCI	p[b]
N	158	57	29	-
< 85 years	104	30[h]	23[i]	-
≥ 85 years	54	27[j]	6[k]	-
Age	83.3 (8.9)	84.1 (7.9)	80.5 (7.8)	0.176
< 85 years	77.6 (3.3)	77.7 (3.4)	77.0 (3.3)	0.701
≥ 85 years	94.3 (5.0)[c]	91.3 (4.4)[c]	94.2 (3.5)	0.029
Female	85 (53.7%)	24 (42.1%)	19 (65.5%)	0.103
< 85 years	55 (52.8%)	12 (40.0%)	16 (69.6%)	0.102
≥ 85 years	30 (55.6%)	12 (44.4%)	3 (50.0%)	0.638
Education	12.1 (3.8)	11.6 (4.1)	11.6 (3.3)	0.610
< 85 years	12.6 (3.9)	11.4 (3.0)	11.6 (3.4)	0.170
≥ 85 years	11.1 (3.4)	11.9 (5.0)	11.7 (2.8)	0.712
MMSE[a]	28.3 (1.3)[d]	27.2 (2.2)[d]	27.8 (1.5)	<0.001
< 85 years	28.6 (1.1)[e,f]	27.8 (1.7)[e]	27.9 (1.5)[f]	0.002
≥ 85 years	27.8 (1.5)[g]	26.5 (2.4)[g]	27.1 (1.7)	0.014
APOE ε4 carrier[m]	29 (19.6%)	16 (30.2%)	6 (22.2%)	0.283
< 85 years	21 (20.4%)	13 (43.3%)	4 (18.2%)	0.028
≥ 85 years	8 (17.8%)	3 (13.4%)	2 (40.0%)	0.361

Data are mean (standard deviation) or n (%).

Abbreviations: aMCI, amnestic mild cognitive impairment; MMSE, mini-mental state examination; naMCI, non-amnestic mild cognitive impairment.

[a] MMSE scores were prorated in 3 participants from a score of 28 or 29. MMSE scores were without any adjustment for age, English speaking background and education.

[b] p-values are of Pearson Chi-square Test or ANOVA.

[c-g] Differences between values of the same superscript were statistically significant ($p < 0.05$).

[h-k] Numbers of participants with single domain MCI were 17, 19, 13 and 4 respectively (in the order from h to k); individuals with single vs. multiple domain MCI did not differ significantly ($p > 0.05$) between age groups.

[m] Excludes 14 participants without APOE data.

Table 2. Mean differences in volumetric MRI measures between cognitive categories. The mean differences of amnestic mild cognitive impairment (aMCI) vs. cognitively normal (CN) and non-amnestic mild cognitive impairment (naMCI) vs. CN are presented in standardized Z scores, adjusted for age, sex and estimated intracranial volumes in the general linear model.

		aMCI Vs CN			naMCI Vs CN			aMCI, naMCI and CN	
	N	Diff	SE	p	Diff	SE	p	F	p
Overall measures									
Cortex	244	**-0.257***	**0.084**	**0.002**	-0.158	0.110	0.153	*5.074*	*0.007*
Anterior CC	237	**-0.375***	**0.131**	**0.005**	-0.167	0.170	0.327	*4.197*	*0.016*
Subcortical ROIs									
Hippocampus	239	**-0.381***	**0.123**	**0.002**	-0.235	0.159	0.141	**5.205**	**0.006**
Thalamus	239	*-0.270**	*0.115*	*0.020*	-0.317*	0.148	0.033	*4.239*	*0.016*
Cortical ROIs									
Entorhinal	240	-0.129	0.131	0.326	-0.488*	0.174	0.005	4.042	0.019

(Table 2) contd…

		aMCI Vs CN			naMCI Vs CN			aMCI, naMCI and CN	
	N	Diff	SE	p	Diff	SE	p	F	p
Isthmus cingulate	239	**-0.341***	**0.128**	**0.008**	-0.152	0.167	0.363	3.629	0.028
Lateral occipital	242	*-0.262**	*0.120*	*0.030*	-0.265	0.157	0.093	3.224	0.042
Parahippocampal	244	**-0.370***	**0.132**	**0.005**	-0.304	0.173	0.080	*4.735*	*0.010*
Pars orbitalis	243	**-0.378***	**0.136**	**0.006**	-0.152	0.179	0.396	3.902	0.022
Pars triangularis	244	**-0.400***	**0.132**	**0.003**	-0.228	0.174	0.192	4.845	*0.009*
Pericalcarine	244	-0.183	0.133	0.169	-0.432*	0.174	0.014	3.505	0.032
Precuneus	241	**-0.296***	**0.113**	**0.010**	-0.129	0.149	0.386	3.474	0.033
Rostral middle frontal	241	-0.229*	0.110	0.039	-0.134	0.146	0.358	2.307	0.102
Superior frontal	244	*-0.250**	*0.107*	*0.021*	0.078	0.141	0.584	3.208	0.042
Superior temporal	244	**-0.325***	**0.108**	**0.003**	-0.225	0.142	0.115	*5.031*	*0.007*
Frontal pole	239	**-0.506***	**0.150**	**0.001**	-0.232	0.197	0.240	*5.829*	*0.003*
Temporal pole	242	*-0.344**	*0.145*	*0.019*	-0.073	0.191	0.701	2.811	0.062
Transverse temporal	244	-0.307*	0.136	0.025	-0.260	0.179	0.148	3.083	0.048

Abbreviations: CC, corpus callosum; Diff, differences; ROIs, regions of interest; SE, standard error.

*Indicate test-wise significant difference between aMCI or naMCI and CN in the general linear model.

Bold values indicate $p < 0.05$ (of 2-tailed T-test) after correction for multiple testing by False Discovery Rate (FDR); *italic values* indicate $p < 0.10$ (of 2-tailed T-test) after FDR correction.

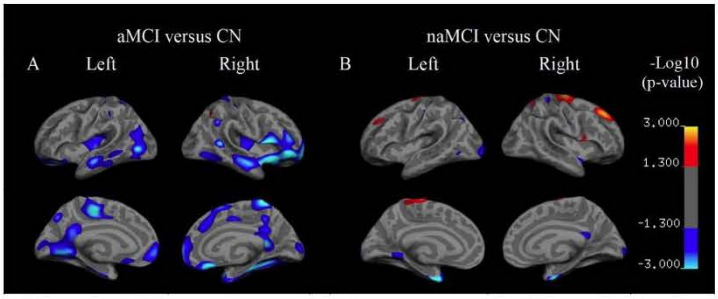

Fig. (2). Surface analysis of the cortical differences between amnestic or non-amnestic mild cognitive impairment (aMCI or naMCI) and normal controls. Results of general linear model testing whether the cortical volume in aMCI (Fig. **2A**) or naMCI (Fig. **2B**) significantly differ from that in normal subjects after controlling for age, sex and estimated intracranial volume (eTIV) are presented. The scale represents values of –Log10 (p-value=0.05-0.001) after correction for multiple testing by False Discovery Rate (FDR). Blue-cyan indicates significant smaller volume in aMCI or naMCI individuals compared to normal; red-yellow indicates the opposite.

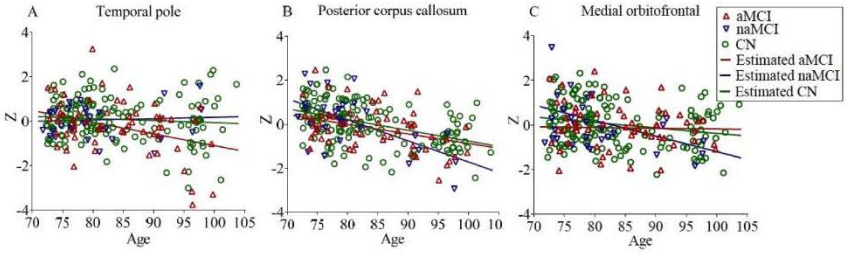

Fig. (3). Linear interactions between cognitive categories and age in select brain regions. Scatter plots of the temporal pole (A), posterior corpus callosum (B) and medial orbitofrontal (C) with the estimated fits in the linear interaction model adjusted for sex and estimated total intracranial volume are presented. Observed values are presented in Z scores. A, temporal pole, differences between amnestic mild cognitive impairment (aMCI) and cognitively normal (CN) participants significantly increased (test-wise p=0.016) with age; B and C, the posterior CC and medial orbitofrontal cortex, distinctions between naMCI and CN significantly increase in these 2 areas with increasing age in the higher age ranges (test-wise p=0.035 and 0.022 respectively).

Table 3. Brain correlates of amnestic mild cognitive impairment (aMCI) in individuals of < 85 and ≥ 85 years respectively. Binary logistic regression analyses were performed to estimate the odds ratio (OR) of volumetric measures in predicting aMCI in the 2 age groups respectively, adjusting for age (within the age group), sex and estimated intracranial volume. All MRI measures were in Z scores; volumes of deep white matter hyperintensities (WMHs) were Ln transformed before Z transformation.

	< 85 years				≥ 85 years			
	N	Wald	OR (95% CI)	p	N	Wald	OR (95% CI)	p
Overall measures								
Cortex[a]	134	7.239	0.270 (0.104-0.701)	0.007	81	1.309	0.592 (0.241-1.454)	0.253
Inferior lateral ventricle[b]	134	0.526	1.204 (0.729-1.986)	0.468	81	1.781	1.425 (0.847-2.396)	0.182
Anterior CC[a,b]	132	2.855	0.633 (0.372-1.076)	0.091	76	2.394	0.582 (0.294-1.155)	0.122
White matter hyperintensities (WMHs)								
Deep WMHs[b]	133	0.465	0.826 (0.476-1.433)	0.495	77	2.131	1.813 (0.816-4.032)	0.144
Subcortical regions of interest (ROIs)								
Hippocampus[a,b]	133	4.652	0.564 (0.335-0.949)	0.031	77	3.782	0.477 (0.226-1.006)	0.052
Thalamus[a,b]	133	3.305	0.574 (0.316-1.044)	0.069	77	2.283	0.603 (0.313-1.162)	0.131
Putamen[a]	125	6.073	0.499 (0.287-0.867)	0.014	58	0.093	1.122 (0.537-2.341)	0.760
Cortical ROIs								
Isthmus cingulate[d]	132	4.908	0.525 (0.297-0.928)	0.027	78	4.625	0.409 (0.181-0.924)	0.032
Parahippocampal[c]	134	7.301	0.463 (0.264-0.809)	0.007	81	1.122	0.722 (0.395-1.320)	0.290
Pars orbitalis[d]	134	4.340	0.571 (0.337-0.967)	0.037	80	2.287	0.642 (0.361-1.140)	0.130
Pars triangularis[d]	134	1.791	0.711 (0.431-1.172)	0.181	81	5.487	0.445 (0.226-0.876)	0.019
Precuneus[c]	134	7.811	0.414 (0.223-0.769)	0.005	78	0.017	1.055 (0.469-2.372)	0.898
Superior frontal[c]	134	6.212	0.425 (0.217-0.833)	0.013	81	0.550	0.735 (0.326-1.657)	0.458
Superior temporal[c]	134	5.987	0.439 (0.227-0.849)	0.014	81	1.291	0.636 (0.291-1.389)	0.256
Frontal pole[c,d]	134	5.944	0.558 (0.349-0.892)	0.015	77	3.163	0.614 (0.359-1.051)	0.075
Temporal pole[d]	134	0.965	0.777 (0.470-1.285)	0.326	79	4.880	0.582 (0.350-0.941)	0.027

Abbreviations: 95% CI, 95% confidence interval; CC: corpus callosum.

[a] Cortex, anterior CC, hippocampus, thalamus and putamen among the overall measures & subcortical ROIs were included in the base model of reduced logistic regression in <85 years.

[b] Inferior lateral ventricle, anterior CC, hippocampus, thalamus and deep WMHs among the overall measures & subcortical ROIs were included in the base model of reduced logistic regression in ≥ 85 years.

[c] Parahippocampal, precuneus, superior frontal, superior temporal and frontal pole cortices among cortical ROIs were included in the base model of reduced logistic regression in <85 years.

[d] Isthmus cingulate, pars orbitalis, pars triangularis, frontal pole and temporal pole cortices among cortical ROIs were included in the base model of reduced logistic regression in ≥ 85 years.

triangularis and temporal polar cortices, with an OR of 0.519 (95% CI: 0.253–1.011) and 0.563 (95% CI: 0.392–1.052) respectively. Interactions between age group and the best discriminators of aMCI (in either <85 or ≥85 years) were also examined in logistic regression, and test-wise significant interaction was noted for the putamen (p=0.025) but not the other discriminators.

4. DISCUSSION

We report a cross-sectional study characterizing brain "atrophy" patterns of aMCI and naMCI in very old individuals, although the reference to "atrophy" here is speculative as it assumes a change from a previous level. The data show that distinctions between MCI and CN in brain structural measures generally persist into advanced age; whereas different MRI markers best discriminate aMCI from CN subjects in <85 and ≥85 age groups respectively. To our knowledge, this is the first study that examines whether the structural MRI biomarkers of aMCI vary with age in the elderly population, and our results give insight into the pathological process underlying aMCI in different age ranges.

Brain "atrophy" associated with aMCI in the full sample was evident in medial temporal structures – the hippocampus and parahippocampal cortex – but also extended to involve the superior temporal cortex and select frontal (pars orbitalis, pars triangularis and frontal pole) and parietal cortical structures (isthmus cingulate and precuneus). While the medial temporal lobe has long been considered as the earliest target of pre-clinical AD, the more widespread structural differences suggest that not all participants with aMCI were at the earliest stage of disease [1, 3, 8, 40]. Of note, the topographic pattern of "atrophy" seen in aMCI overlaps largely with the default mode network, a specific set of brain areas that are active when the individual is at wakeful rest [41]. Such an overlap is in agreement with previous studies of either structural imaging [38] or functional connectivity [42, 43], indicating greater vulnerability of the default mode network to pathologies associated aMCI. The relatively spared entorhinal cortex in aMCI is however unexpected [1, 3, 44]. Since the entorhinal cortex occupies only a small adjacent area on the medial temporal surface, the negative result might be ascribed to a higher level of variability compared with other cortical areas due to difficulties in the surface reconstruction, and such variability may increase with age [45].

The "atrophy" of the anterior CC in aMCI in our sample is in agreement with one recent meta-analysis, which suggests the anterior part (rostrum and genu) being more indicative of MCI status compared to the remaining CC [46]. However, such finding does not seem to fully overlap with the features observed in AD. The association between atrophy or microstructure changes of CC and AD has been reported as "region-specific", i.e. mostly involving both the anterior (rostrum, genu) and posterior (splenium) areas [47-49]. Since fibers that selectively innervate the temporo-parietal regions cross through posterior CC, some authors even considered the splenium more sensitive of AD in its preclinical stage [48, 50-52]. Involvement of the anterior CC, where comprises fibers curving forward into the frontal neocortex, has been more implicated in frontal WMHs [47] and vascular cognitive impairment [53]. It should also be mentioned that the atrophy of anterior CC has been associated with many other aging-related pathologies, such as frontotemporal lobe degeneration [54], Parkinsonian disorders [55] and multiple system atrophy [56]. Thus the "atrophy" of anterior CC is likely to be a non-specific maker of aMCI, reflecting varying pathologies, alone or in combination, among which vascular origin appears to be an important contributor.

WMHs – another marker of vascular pathology – did not differ significantly between cognitive categories in this study. A few reasons could account for the negative results. First, strategic locations of vascular pathology, such as WMHs located at anterior thalamic radiation, might be more important than the overall burden of WMHs in predicting cognitive status [57]. Second, vascular pathologies may be more indicative of specific cognitive impairment such as deficits in processing speed or executive function rather than cognitive categories, in particular in prodromal stage of dementia [58]. Third, incorporating a variety of vascular pathologies, i.e. lacunae, micro-infarcts and micro-bleeds in addition to WMHs, may increase the sensitivity of the analysis [14, 59].

Distinctions between aMCI and CN were generally found to persist into advanced age. When the two age groups were examined separately, however, the brain regions that best discriminated aMCI from normal were different in the <85 and ≥85 years group. It should be pointed out that the interactions between age group and discriminators, with one exception, were not statistically significant; and this is consistent with the general linear analyses. Still, the optimal set of markers (Table **4**) represents the selection of brain areas that,

Table 4. Brain regions that are most indicative of amnestic mild cognitive impairment (aMCI) in the <85 and ≥85 years respectively. Reduced logistic regression models were applied using backward elimination strategies. Analyses were performed on cortical regions of interest (ROIs) and the remains of volumetric measurements respectively by age groups.

	< 85 years			≥ 85 years		
	Wald	**OR (95% CI)**	**p**	**Wald**	**OR (95% CI)**	**p**
Overall & subcortical ROIs						
Cortex	2.853	0.418 (0.152–1.150)	0.091	-	-	-
Putamen	2.986	0.595 (0.330–1.072)	0.084	-	-	-
Hippocampus	-	-	-	3.782	0.477 (0.226–1.006)	0.052
Cortical ROIs						
Parahippocampal	5.818	0.488 (0.272–0.874)	0.016	-	-	-
Precuneus	3.328	0.546 (0.285–1.046)	0.068	-	-	-
Superior frontal	5.055	0.427 (0.203–0.897)	0.025	-	-	-
Pars triangularis	-	-	-	3.089	0.519 (0.253–1.011)	0.054
Temporal pole	-	-	-	4.099	0.563 (0.392–1.052)	0.079

Abbreviations: 95% CI, 95% confidence interval; OR: odds ratio.

in combination, discriminate most strongly between aMCI and normal individuals within the two age groups, with possible clinical implications.

In those <85 years, the best indicators of aMCI were small volumes of the overall cortex, putamen, parahippocampal gyrus, precuneus and superior frontal cortex. These regions comprise key structures of the temporo-parietal memory system (parahippocampus and precuneus) and the fronto-striatal (superior frontal cortex and putamen) networks [38]. Although atrophy in both systems commonly co-occur, they are thought to arise from dissociated factors, i.e. the former is regarded characteristic of AD and the latter is associated with mild cognitive decline in normal aging [60, 61]. Such pattern is consistent with the unstable nature of MCI diagnosis. Approximately one third of the aMCI subjects reverted to normal cognition at 2-year follow up in the MAS base sample, while a small proportion of individuals with aMCI converted to dementia [62]. Both the neuroimaging finding and clinical outcomes suggest heterogeneous underpinnings of aMCI, i.e. the most common age-related and AD-related brain changes.

In the very old (≥85 years), hippocampus, pars triangularis and temporal pole were found to be the best discriminators of aMCI from normal subjects. Higher age has been associated with greater hippocampal atrophy in AD, recognized as the "limbic-predominant" subtype, from both neuropathological and neuroimaging studies; whereas younger AD patients with onset in their 60s or early 70s are prone to be affected with widespread cortical atrophy [63, 64]. These age-related topographic patterns of AD could account for some of the differences noted. Hippocampal involvement in those cognitively impaired has also been associated with other pathologies, such as hippocampal sclerosis [13, 15], Lewy-related pathology and argyrophilic grain disease [15], of which the prevalence increases steadily with age. Therefore, hippocampal atrophy appears to be sensitive to early cognitive impairment in the very old, but not necessarily specific to the pathological process of AD. The two cortical markers – pars triangularis and temporal pole – are noteworthy, as they are not typical hallmarks of aMCI or early AD [1, 8]. A few possible explanations are considered here. The pars triangularis composes an important part of the ventrolateral prefrontal cortex, being implicated in cognitive control, i.e. to "bring knowledge to mind that is relevant to current goals and to enable flexible cognition and action" [65]. In young elders, atrophy of this area has been related to poorer executive function (response inhibition, working memory and task switching) [66], which may further affect performance on memory tasks [38, 60]. Although at advanced age, the overall high prevalence of amyloid deposition and/or neurodegenerations could result in cognitive impairment [67], preservation of the pars triangularis may help to compensate against subtle cognitive deficits via adequate cognitive control, thus enable better neuropsychological performance. Furthermore, both pars triangularis and temporal pole are implicated in speech/language processing [68] as well as social or "person-related" cognition [69, 70]. It is possible that preservation of these regions could be related to a higher level of social engagement and/or cognitively stimulating activities, which may confer protection against cognitive decline in the very old [71]. A better understanding of the neurobiological underpinnings of cognition at advanced age is warranted, and the structural brain patterns and their relationship with clinical characteristics in CN elders may inform appropriate strategies in preventing or delaying cognitive impairment in late life.

Distinctions between naMCI and CN in the study are generally of small effect size and non-significant after correction for multiple testing. The lack of robust findings may be ascribed to the heterogeneous nature of underlying disorder [7, 9] and inadequate sample size of naMCI in this study. One exception is the significant atrophy in entorhinal cortex in naMCI participants compared to normal. This finding mainly related to the <85 group, possibly because the number of individuals with naMCI in the ≥85 group was small. The cross-sectional nature of our study does not permit an assessment of the significance of this finding. It has been shown that naMCI is also at increased risk of conversion to dementia such as AD [72-74], and the involvement of the entorhinal cortex is indicative of early AD pathology [8]. The lack of significant memory impairment may be due to compensatory mechanisms in these individuals.

This study has a number of limitations. First, it is cross-sectional and therefore cannot account for baseline cognitive function and brain volumetrics. Longitudinal studies would be able to provide a more definite analysis of the difference between cognitive categories with increasing age, yet there are practical difficulties in conducting such studies over an extended period of time. Second, the study includes participants from two cohorts, i.e. MAS and SCS. While both studies were conducted in the same geographical regions with similar methodologies, some differences in the instruments used were inevitable as neuropsychological batteries appropriate for the young elderly are generally poorly tolerated by the very old. The differentiation between dementia, MCI and CN in the very old therefore becomes more difficult. We dealt with this by only including participants with sufficient data for classification to proceed and used expert consensus to deal with inadequate normative data for some tests. Third, some sampling bias in such studies is inevitable. Participants who agree to undergo a research MRI are generally in better physical and cognitive health than those who decline this procedure. This difference becomes more evident with increasing age, thus making the very old participants less representative of the population. Fourth, the surface-based segmentation techniques in neuroimaging suffer from some limitations. The accuracy of the volume estimation is known to vary across the cortical surface due to lower contrast-to-noise ratio in specific regions such as entorhinal cortex [45] as well as the decreasing grey/white ratio with advanced age [75]. Application of these neuroimaging techniques in the very old does result in more manual correction than that seen in younger participants, possibly introducing error.

CONCLUSION

Our study provides additional insights into the structural MRI markers of aMCI and naMCI in an elderly population aged 71 to 103 years, and how this might be different in relatively young and very old individuals. The study shows that brain volumetrics continue to differentiate aMCI from CN into advanced age. The brain regions that best discriminate

the two categories, however, do differ between <85 and ≥85 years, and this suggests differences in the underpinnings of cognitive impairment at different ages.

LIST OF ABBREVIATIONS

AD	=	Alzheimer's disease
ANOVA	=	analysis of variance
aMCI	=	amnestic mild cognitive impairment
BADLs	=	Bayer activities of daily living scale
CC	=	corpus callosum
CI	=	confidence interval
CN	=	cognitively normal
Diff	=	difference
eTIV	=	estimated total intracranial volume
FLAIR	=	fluid attenuated inversion recovery
GM	=	grey matter
MAS	=	Sydney Memory and Ageing Study
MCI	=	mild cognitive impairment
MMSE	=	Mini-Mental State Examination
MRI	=	magnetic resonance imaging
naMCI	=	non-amnestic mild cognitive impairment
OR	=	odds ratio
ROIs	=	regions of interest
SCS	=	Sydney Centenarian Study
SD	=	standard deviation
SE	=	standard error
WM	=	white matter
WMHs	=	white matter hyperintensities

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AUTHORS' CONTRIBUTIONS

ZY wrote first the draft, revised the manuscript in its final form, conceptualized the study, and contributed to the data acquisition, analysis and interpretation. WW conceptualized the study, and contributed to data interpretation and manuscript preparation. JJ contributed to the acquisition and interpretation of data. JDC conceptualized the study, performed the statistical analysis and contributed to data interpretation and manuscript preparation. SR and CL supervised data acquisition and contributed to data interpretation and manuscript preparation. MJS obtained the funding, conceptualized the study, supervised data acquisition and contributed to manuscript preparation. NAK obtained funding, supervised data acquisition and contributed to data analysis and interpretation, and manuscript preparation. RLR, HB and JNT obtained funding, conceptualized the study, supervised data acquisition and contributed to manuscript preparation. PSS obtained funding, conceptualized the study, supervised analysis and data interpretation and finalized the manuscript.

SUPPLEMENTARY MATERIAL

Supplementary Table 1. Brief comparison between the included and the remaining participants of the Sydney Centenarian Study and Memory and Aging Study respectively.

Supplementary Table 2. Mean differences in volumetric MRI measures between cognitive categories in all the regions of interest.

Supplementary Table 3. Brain correlates of amnestic mild cognitive impairment (aMCI) in individuals of <85 and ≥85 years respectively in all the regions of interest.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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Supplementary Table 5.1. Brief comparison between the included and the remaining participants of SCS and MAS.

	Sydney Centenarian Study (SCS)				Memory and Ageing Study (MAS)			
	SCS included	SCS baseline remaining	F/χ^2	p	MAS included	MAS baseline remaining	F/χ^2	p
N	42	323			202	835		
Age, years / mean (SD)	97.8 (1.8)	97.4 (2.1)	1.439	0.231	80.1 (5.8)	78.7 (4.8)	10.845	0.001
Sex, female %	45.2%	72.4%	12.936	0.001	54.0%	55.4%	0.146	0.703
Education, years / mean (SD)	11.0 (3.5)	10.4 (3.2)[a]	0.987	0.321	12.1 (3.8)	11.5 (3.4)	6.383	0.012
MMSE scores / mean (SD)	27.2 (2.1)	21.7 (5.9)[b]	42.27	<0.001	28.2 (1.5)	28.0 (1.6)	0.244	0.621
APOE ε4 carrier, N (%)	6 (20%)[c]	28 (13.8%)[d]	0.808	0.405	45 (22.7%)[k]	176 (22.4%)[q]	0.007	0.924
Medical comorbidities, N (%)								
Stroke	4 (9.5%)	17 (5.6%)[e]	0.963	0.306	3 (1.5%)[r]	39 (4.7%)[s]	4.205	0.045
Transient ischemic attack	3 (7.7%)[f]	35 (11.9%)[g]	0.604	0.595	11 (5.6%)[t]	60 (7.3%)[u]	0.777	0.44
Coronary artery disease	56 (18.7%)	8 (19.1%)[h]	0.004	0.953	22 (11%)[n]	177 (21.4%)[w]	11.067	0.001
Hypertension	22 (53.7%)[i]	132 (44.4%)[j]	1.233	0.316	117 (58.2%)[n]	514 (61.8%)[k]	0.868	0.375
High cholesterol	11 (28.2)[k]	58 (19.5%)[l]	1.59	0.21	114 (56.7%)[i]	509 (61.2%)[k]	1.346	0.261
Diabetes mellitus	4 (9.5%)	19 (6.3%)[m]	0.618	0.504	13 (6.4%)	113 (13.6%)[x]	7.811	0.004
Smoking	16 (38.1%)	93 (31.0%)[h]	0.854	0.379	104 (52.0%)[n]	455 (54.5%)[i]	0.424	0.528
Depression	1 (2.5%)[n]	12 (4.3%)[o]	0.302	0.582	32 (15.9%)[i]	132 (16.5%)[y]	0.037	0.915

[a-y]Missing data (N): a=25, b=29, c=12, d=120, e=22, f=3, g=29, h=23, i=1, j=26, k=3, l=26, m=21, n=2, o=47, q=51, s=8, t=4, u=17, w=6, x=5, y=34.

Supplementary Table 5.2. Mean differences in volumetric MRI measures between cognitive categories.

Overall measures		aMCI Vs CN			naMCI Vs CN			aMCI, naMCI and CN	
	N	Diff	SE	p	Diff	SE	p	F	p
Cortex	244	**-0.257***	**0.084**	**0.002**	-0.158	0.110	0.153	*5.074*	*0.007*
Cortical WM	241	-0.103	0.101	0.311	0.015	0.133	0.908	0.564	0.569
Subcortical GM	232	-0.231	0.135	0.088	-0.270	0.172	0.119	2.273	0.105
Lateral Ventricle	244	0.103	0.131	0.431	0.203	0.172	0.237	0.867	0.421
Inferior Lateral Ventricle	244	0.193	0.132	0.143	0.173	0.173	0.318	1.351	0.261
3rd and 4th Ventricle	244	0.113	0.121	0.350	0.213	0.159	0.182	1.138	0.322
Cerebellum Cortex	244	-0.024	0.111	0.829	0.079	0.145	0.588	0.199	0.819
Cerebellum WM	244	-0.125	0.131	0.341	-0.292	0.173	0.092	1.640	0.196
Brain Stem	244	-0.011	0.127	0.933	-0.126	0.166	0.448	0.291	0.748
Anterior CC	237	**-0.375***	**0.131**	**0.005**	-0.167	0.170	0.327	*4.197*	*0.016*
Posterior CC	239	-0.187	0.134	0.164	-0.046	0.175	0.793	0.975	0.379
White matter hyperintensities (WMHs)									
Periventricular WMHs	237	0.031	0.150	0.834	-0.066	0.198	0.739	0.094	0.910
Deep WMHs	237	0.026	0.128	0.839	0.006	0.169	0.972	0.021	0.979
Subcortical Regions of Interest (ROIs)									
Hippocampus	239	**-0.381***	**0.123**	**0.002**	-0.235	0.159	0.141	**5.205**	**0.006**
Amygdala	210	-0.005	0.165	0.976	-0.221	0.202	0.274	0.616	0.541
Thalamus	239	*-0.270**	*0.115*	*0.020*	-0.317*	0.148	0.033	*4.239*	*0.016*

(Supplementary table 5.2. Continued)

Accumbens-Caudate	236	0.108	0.131	0.408	-0.294	0.170	0.084	2.180	0.115
Putamen	208	-0.223	0.137	0.105	-0.164	0.178	0.357	1.527	0.220
Pallidum	206	0.032	0.156	0.840	-0.028	0.202	0.891	0.036	0.964
Cortical ROIs									
BanksSTS	244	-0.071	0.127	0.575	0.048	0.167	0.773	0.239	0.788
Caudal anterior cingulate	237	0.000	0.151	0.998	-0.006	0.196	0.976	0.000	1.000
Caudal middle frontal	243	-0.079	0.127	0.534	-0.114	0.167	0.494	0.361	0.698
Cuneus	244	-0.229	0.131	0.082	-0.159	0.173	0.357	1.705	0.184
Entorhinal	240	-0.129	0.131	0.326	-0.488*	0.174	0.005	4.042	0.019
Fusiform	242	-0.203	0.111	0.068	-0.244	0.146	0.096	2.588	0.077
Inferior parietal	244	-0.022	0.115	0.851	-0.131	0.151	0.386	0.377	0.686
Inferior temporal	239	-0.050	0.116	0.666	-0.262	0.155	0.092	1.438	0.239
Isthmus cingulate	239	**-0.341***	**0.128**	**0.008**	-0.152	0.167	0.363	3.629	0.028
Lateral occipital	242	*-0.262**	*0.120*	*0.030*	-0.265	0.157	0.093	3.224	0.042
Lateral orbitofrontal	241	-0.185	0.111	0.098	-0.020	0.145	0.891	1.394	0.250
Lingual	244	-0.240	0.132	0.070	-0.247	0.173	0.154	2.269	0.106
Medial orbitofrontal	241	-0.140	0.121	0.246	0.055	0.157	0.729	0.841	0.432
Middle temporal	241	-0.212	0.109	0.052	-0.114	0.145	0.434	2.003	0.137
Parahippocampal	244	**-0.370***	**0.132**	**0.005**	-0.304	0.173	0.080	*4.735*	*0.010*
Paracentral	243	-0.222	0.129	0.087	0.237	0.170	0.164	3.008	0.051
Pars opercularis	244	-0.160	0.126	0.208	0.079	0.166	0.636	1.061	0.348

(Supplementary table 5.2. Continued)

Pars orbitalis	243	**-0.378***	**0.136**	**0.006**	-0.152	0.179	0.396	3.902	0.022
Pars triangularis	244	**-0.400***	**0.132**	**0.003**	-0.228	0.174	0.192	4.845	*0.009*
Pericalcarine	244	-0.183	0.133	0.169	-0.432*	0.174	0.014	3.505	0.032
Postcentral	244	-0.172	0.121	0.158	-0.079	0.159	0.621	1.032	0.358
Posterior cingulate	241	-0.056	0.129	0.667	-0.068	0.169	0.691	0.145	0.865
Precentral	244	-0.145	0.117	0.216	0.011	0.153	0.941	0.817	0.443
Precuneus	241	**-0.296***	**0.113**	**0.010**	-0.129	0.149	0.386	3.474	0.033
Rostral anterior cingulate	240	-0.116	0.134	0.388	-0.093	0.173	0.591	0.448	0.639
Rostral middle frontal	241	-0.229*	0.110	0.039	-0.134	0.146	0.358	2.307	0.102
Superior frontal	244	*-0.250**	*0.107*	*0.021*	0.078	0.141	0.584	3.208	0.042
Superior parietal	244	-0.084	0.116	0.469	-0.238	0.153	0.121	1.305	0.273
Superior temporal	244	**-0.325***	**0.108**	**0.003**	-0.225	0.142	0.115	*5.031*	*0.007*
Supramarginal	244	-0.072	0.118	0.545	0.162	0.155	0.299	0.877	0.417
Frontal pole	239	**-0.506***	**0.150**	**0.001**	-0.232	0.197	0.240	*5.829*	*0.003*
Temporal pole	242	*-0.344**	*0.145*	*0.019*	-0.073	0.191	0.701	2.811	0.062
Transverse temporal	244	-0.307*	0.136	0.025	-0.260	0.179	0.148	3.083	0.048
Insula	241	-0.200	0.118	0.093	-0.039	0.156	0.805	1.426	0.242

The mean differences of amnestic mild cognitive impairment (aMCI) vs. cognitively normal (CN) and non-amnestic mild cognitive impairment (naMCI) vs. CN are presented in standardized Z scores, adjusted for age, sex and estimated intracranial volumes in the general linear model. Volumes of white matter hyperintensities were Ln transformed before converting into Z scores.

*indicate test-wise significant difference in the general linear model.

Abbreviation: aMCI, amnestic mild cognitive impairment; BanksSTS, banks of superior temporal sulcus; CC, corpus callosum; CN, cognitively normal; Diff, difference; GM, grey matter; naMCI, non- amnestic mild cognitive impairment; ROIs, regions of interest; SE, standard error; WM, white matter; WMHs, white matter hyperintensities.

Bold values indicate $p<0.05$ (of 2-tailed T-test) after corrected for multiple testing using False Discovery Rate (FDR); *italic values* indicate $p<0.10$ (of 2-tailed T-test) after FDR correction.

Supplementary Table 5.3. Brain correlates of amnestic mild cognitive impairment (aMCI) in individuals of <85 and ⩾85 years respectively.

Overall measures	<85 years				≥85 years			
	N	Wald	OR (95% CI)	p	N	Wald	OR (95% CI)	p
Cortex[a]	134	7.239	0.270 (0.104-0.701)	0.007	81	1.309	0.592 (0.241-1.454)	0.253
Cortical WM	133	2.058	0.608 (0.308-1.200)	0.151	79	0.395	1.316 (0.559-3.097)	0.529
Subcortical GM	134	3.891	0.596 (0.357-0.997)	0.049	70	0.033	0.938 (0.468-1.878)	0.856
Lateral Ventricle	134	0.470	1.197 (0.715-2.004)	0.493	81	0.008	1.025 (0.593-1.773)	0.928
Inferior Lateral Ventricle[b]	134	0.526	1.204 (0.729-1.986)	0.468	81	1.781	1.425 (0.847-2.396)	0.182
3rd and 4th Ventricle	134	0.774	1.272 (0.744-2.175)	0.379	81	0.025	1.048 (0.587-1.870)	0.875
Cerebellum Cortex	134	0.008	0.974 (0.548-1.730)	0.929	81	0.006	0.972 (0.458-2.060)	0.940
Cerebellum WM	134	0.257	0.889 (0.565-1.399)	0.612	81	0.770	0.752 (0.698-1.421)	0.380
Brain Stem	134	0.082	1.078 (0.648-1.809)	0.775	81	0.239	0.854 (0.454-1.608)	0.625
Anterior CC[a,b]	132	2.855	0.633 (0.372-1.076)	0.091	76	2.394	0.582 (0.294-1.155)	0.122
Posterior CC	133	2.458	0.677 (0.416-1.102)	0.117	77	0.322	0.821 (0.416-1.622)	0.571
White matter hyperintensities (WMHs)								
Periventricular WMHs	133	0.499	0.864 (0.575-1.297)	0.480	77	1.126	1.452 (0.729-2.893)	0.289
Deep WMHs[b]	133	0.465	0.826 (0.476-1.433)	0.495	77	2.131	1.813 (0.816-4.032)	0.144
Subcortical regions of interest (ROIs)								
Hippocampus[a,b]	133	4.652	0.564 (0.335-0.949)	0.031	77	3.782	0.477 (0.226-1.006)	0.052
Amygdala	130	0.151	0.918 (0.597-1.412)	0.697	53	0.128	1.138 (0.561-2.308)	0.721

(Supplementary table 5.3. continued)								
Thalamus[a,b]	133	3.305	0.574 (0.316-1.044)	0.069	77	2.283	0.603 (0.313-1.162)	0.131
Accumbens_Caudate	130	0.103	1.086 (0.654-1.804)	0.749	78	0.392	1.262 (0.610-2.611)	0.531
Putamen[a]	125	6.073	0.499 (0.287-0.867)	0.014	58	0.093	1.122 (0.537-2.341)	0.760
Pallidum	126	0.107	1.082 (0.674-1.738)	0.743	55	0.001	1.003 (0.556-1.810)	0.993
Cortical ROIs								
BanksSTS	134	0.441	0.846 (0.516-1.387)	0.507	81	0.448	1.258 (0.642-2.464)	0.503
Caudal anterior cingulate	131	0.001	0.994 (0.656-1.504)	0.976	77	0.266	1.160 (0.659-2.042)	0.606
Caudal middle frontal	134	0.400	0.846 (0.504-1.420)	0.527	80	0.056	0.927 (0.494-1.740)	0.812
Cuneus	134	1.979	0.701 (0.427-1.150)	0.160	81	0.821	0.715 (0.346-1.477)	0.365
Entorhinal	134	0.726	0.804 (0.488-1.327)	0.394	78	0.756	0.756 (0.402-1.421)	0.385
Fusiform	134	2.350	0.637 (0.358-1.134)	0.125	79	0.388	0.788 (0.372-1.668)	0.533
Inferior parietal	134	0.114	0.902 (0.494-1.645)	0.736	81	0.542	1.279 (0.664-2.464)	0.461
Inferior temporal	134	0.002	0.987 (0.555-1.753)	0.963	77	0.012	0.966 (0.521-1.791)	0.912
Isthmus cingulate[d]	132	4.908	0.525 (0.297-0.928)	0.027	78	4.625	0.409 (0.181-0.924)	0.032
Lateral occipital	134	2.099	0.677 (0.400-1.147)	0.147	79	0.554	0.758 (0.365-1.573)	0.457
Lateral orbitofrontal	134	1.230	0.713 (0.392-1.297)	0.267	78	1.059	0.690 (0.340-1.400)	0.303
Lingual	134	4.759	0.586 (0.362-0.947)	0.029	81	0.244	1.197 (0.586-2.445)	0.621
Medial orbitofrontal	134	3.403	0.578 (0.323-1.035)	0.065	78	0.182	1.154 (0.598-2.224)	0.670
Middle temporal	134	3.059	0.566 (0.299-1.071)	0.080	79	0.003	1.022 (0.483-2.163)	0.954
Parahippocampal[c]	134	7.301	0.463 (0.264-0.809)	0.007	81	1.122	0.722 (0.395-1.320)	0.290
Paracentral	134	2.430	0.638 (0.363-1.122)	0.119	80	1.738	0.657 (0.352-1.227)	0.187

(Supplementary table 5.3. continued)

Pars opercularis	134	0.913	0.775 (0.460-1.307)	0.339	81	0.364	0.827 (0.446-1.533)	0.546
Pars orbitalis[d]	134	4.340	0.571 (0.337-0.967)	0.037	80	2.287	0.642 (0.361-1.140)	0.130
Pars triangularis[d]	134	1.791	0.711 (0.431-1.172)	0.181	81	5.487	0.445 (0.226-0.876)	0.019
Pericalcarine	134	5.329	0.511 (0.288-0.903)	0.021	81	1.004	1.321 (0.766-2.277)	0.316
Postcentral	134	0.936	0.773 (0.459-1.302)	0.333	81	1.719	0.570 (0.246-1.320)	0.190
Posterior cingulate	133	0.884	0.795 (0.493-1.282)	0.347	79	0.313	1.207 (0.624-2.333)	0.576
Precentral	134	2.132	0.668 (0.388-1.148)	0.144	81	0.081	0.906 (0.457-1.794)	0.777
Precuneus[c]	134	7.811	0.414 (0.223-0.769)	0.005	78	0.017	1.055 (0.469-2.372)	0.898
Rostral anterior cingulate	134	0.730	0.814 (0.509-1.305)	0.393	77	0.005	1.026 (0.516-2.040)	0.943
Rostral middle frontal	134	2.867	0.578 (0.306-1.090)	0.090	79	0.302	0.808 (0.377-1.730)	0.583
Superior frontal[c]	134	6.212	0.425 (0.217-0.833)	0.013	81	0.550	0.735 (0.326-1.657)	0.458
Superior parietal	134	1.087	0.739 (0.418-1.305)	0.297	81	0.040	1.076 (0.526-2.197)	0.842
Superior temporal[c]	134	5.987	0.439 (0.227-0.849)	0.014	81	1.291	0.636 (0.291-1.389)	0.256
Supramarginal	134	1.313	0.689 (0.365-1.303)	0.252	81	0.004	0.979 (0.506-1.894)	0.950
Frontal pole[c,d]	134	5.944	0.558 (0.349-0.892)	0.015	77	3.163	0.614 (0.359-1.051)	0.075
Temporal pole[d]	134	0.965	0.777 (0.470-1.285)	0.326	79	4.880	0.582 (0.350-0.941)	0.027
Transverse temporal	134	4.023	0.623 (0.392-0.989)	0.045	81	1.238	0.700 (0.374-1.312)	0.266
Insula	134	0.615	0.802 (0.462-1.392)	0.433	79	1.575	0.613 (0.285-1.316)	0.209

Binary logistic regression analyses were performed to estimate the odds ratio (OR) of volumetric measures in predicting aMCI in the 2 age groups respectively, adjusting for age (within the age group), sex and estimated intracranial volume. All MRI measures were in Z scores;

volumes of white matter hyperintensities were Ln transformed before Z transformation.

Abbreviation: aMCI, amnestic mild cognitive impairment; BanksSTS, banks of superior temporal sulcus; CC, corpus callosum; CI, confidence interval; GM, grey matter; OR, odds ratio; ROIs, regions of interest; WM, white matter; WMHs, white matter hyperintensities.

[a]cortex, anterior CC, hippocampus, thalamus and putamen among the overall measures & subcortical ROIs were included in the base model of reduced logistic regression in <85 years;

[b]inferior lateral ventricle, anterior CC, hippocampus, thalamus and deep WMHs among the overall measures & subcortical ROIs were included in the base model of reduced logistic regression in 85+ years;

[c]parahippocampal, precuneus, superior frontal, superior temporal and frontal pole cortices among cortical ROIs were included in the base model of reduced logistic regression in <85 years;

[d]isthmus cingulate, pars orbitalis, pars triangularis, frontal pole and temporal pole cortices among cortical ROIs were included in the base model of reduced logistic regression in 85+ years.

5.3 Summary of main findings

Structural MRI distinguished aMCI, but not naMCI, from cognitively normal individuals from 71 to 103 years. MRI markers of aMCI included smaller volumes of the medial temporal lobe, and select frontal and parietal cortices. The volume of WMHs was not significantly associated with aMCI or naMCI in our sample.

The MRI markers that best differentiated aMCI from normal, however, differed between the young old (< 85 years) and oldest old (≥ 85 years) groups, i.e., the superior frontal cortex, putamen, parahippocampus and precuneus in the young old, and hippocampus, pars triangularis and temporal pole in the oldest old, suggesting distinct neurobiological underpinnings of aMCI between the two age groups.

CHAPTER 6: GENERAL DISCUSSION AND FUTURE DIRECTIONS

The overarching aim of this thesis was to examine structural MRI profiles of the aged brain, in particular those of the oldest old. The studies comprising the thesis focused on the following: 1) the brain MRI profiles of non-demented individuals beyond 90 years; 2) MRI markers of dementia at 80 and 95 years respectively, and moderating effects of age on the association of MRI measures with dementia status; and 3) MRI signature of MCI in late life, and markers that best distinguish aMCI from normal cognition in the young old (< 85 years) and oldest old (≥ 85 years).

6.1 Non-demented brain aging in late life

In Chapter 3, linear negative relationships of age with MRI-derived measures of grey matter were observed from 8^{th} to 11^{th} decades of life, in concordance with most cross-sectional studies in younger elderly [1-5]. Nevertheless, the non-demented 90-plus individuals were found to have a "temporal-posterior" pattern of brain loss, that is, greatest effects of age being in the medial temporal lobe, and parietal and occipital cortices. Of note, this pattern encapsulated almost entirely the primary somatosensory, visual and auditory cortices, plus the primary motor cortex of the frontal lobe, sparing the "anterior" part of the brain. Using a subsample of high-functioning individuals who did not have evidence of MCI, a similar pattern was observed, suggesting that it is age-related rather than disease-related.

This "temporal-posterior" distribution was different from the established "frontal-temporal" pattern in healthy younger elderly (60-90 years) [6]. Such discrepancy could at least be partially ascribed to differences in sample age span. A similar "temporal-

occipital" pattern was reported in the Rotterdam Scan Study (60-97 years), despite the fact that only 15 individuals of 90-plus were included and only cortical thickness of the four lobes was examined [4]. Another longitudinal sample (23-87 years) reported accelerating atrophy of temporal and occipital cortices with increasing age [7], which support the findings in this thesis. However, none of the previous studies examined specifically the brain MRI profiles of the 90-plus, by using high-resolution structural MRI and the inclusion of a wide range of volumetric and thickness measures. The study as described in Chapter 3 has, therefore, bridged the knowledge gap and extended current understanding of the successfully aged brains in the 10^{th} and 11^{th} decades of life.

The "temporal-posterior" pattern of brain loss at advanced age could only be partly explained by the "last in, first out" or "retrogenesis" hypothesis [8, 9], with early maturing cortices, such as the primary sensory and motor cortices, being affected during the very late stage of ageing. This was also consistent with the high prevalence of sensory impairment and physical disability in the oldest old, even though these individuals remain dementia-free [10]. However, the prefrontal cortex, an area of late maturation and high complexity, was relatively spared in these very elderly individuals, suggesting that the "last in" cortex may not necessarily be "first out" in successful cognitive ageing.

Another important finding was the non-linear relationship of age with white matter hyperintensities (WMHs), with the most extensive accumulation of deep WMHs being in the non-demented 90-plus population. While WMHs have been related to hypertension and other cardiovascular risk factors in the young old [11], such association was non-significant in our sample of older individuals. This was observed in both the non-demented and high-functioning samples. The pathogenesis and clinical

significance of the WMHs at advanced age remain unclear, and the influence on physical and mental health warrant further investigation.

Taken together, the structural MRI profile of the non-demented 90-plus population is characterised by a "temporal-posterior" pattern of grey matter loss and prominent accumulation of WMHs, particularly deep WMHs. This established profile could serve as the neuroanatomical basis for understanding successful cognitive ageing at advanced ages.

6.2 MRI markers of clinical dementia

The principal findings of the study described in Chapter 4 were: 1) thin cortex and small hippocampus were strongly related to dementia at 80 and 95 years; whereas vascular markers, the WMHs and brain infarcts, were independent indicators of dementia at 80 but not at 95 years; 2) a composite MRI pathology index (hereafter "pathology index") was a marker of dementia, yet its predictive power was much less at 95 than at 80 years.

The finding on the MRI markers of dementia at the age of 95 was consistent with previously published data, albeit limited. In the Vantaa 85+ Study, medial temporal atrophy and WMHs were examined on post-mortem MRI, and only the former [12] was found to be a marker of dementia in the 85-plus population [13]. Similarly in the Sydney Older Person Study (mean age 85.5 years), WMHs on MRI were found to have little impact on cognition [14]. A population-based neuropathology study has also suggested that pathologically defined atrophy of cortex and hippocampus, but not the vascular pathology, was indicative of dementia at 95 years [15]. However, many of the neuroimaging studies used grading scores, instead of continuous measures, to indicate the severity of hippocampal atrophy or WMHs. Moreover, none of them had examined cortical regions or subcortical nuclei other than hippocampus. Hence, using a broad

range of continuous MRI-derived brain measures, this present study has supported and extended the current understanding of the MRI markers of dementia in the oldest old. Together with the findings in Chapter 3, this thesis has provided strong evidence that brain vascular injuries are common and are not independently associated with dementia status at advanced ages.

Mixed brain pathologies are regarded as a strong predictor of dementia in neuroimaging and pathological studies, in both the young old and oldest old [16-18], yet the moderating effect of age was previously under-examined. A few neuropathology studies suggested that the relationship between brain pathology (AD pathology alone or in combination with brain infarcts) and dementia weakened at advanced age [15, 19]; whereas others argued that the attenuated association was probably due to incomplete assessment of the varying neurodegenerations or vascular injuries, since neuropathological comorbidity is common in the oldest old [20, 21]. These concerns could be partly addressed by the use of atrophy indices on structural MRI as surrogates of the overall burden of neurodegenerations [12, 22-24]. Combined with quantitative assessment of vascular injuries, the pathology index established in Chapter 4 is likely to reflect the accumulative effects of brain pathologies. Still, its association with clinical dementia was found to be much weaker at 95 than at 80 years, adding further support to the notion that the clinical significance of brain injuries is attenuated at more advanced age, and additional factors may contribute to the clinical expression of dementia.

6.3 MRI signatures of MCI

Chapter 5 shows that structural MRI distinguished aMCI, but not naMCI, from normal individuals in our sample, from 8^{th} to 11^{th} decades of life. MRI markers of aMCI included smaller volumes of the medial temporal lobe, and select frontal and parietal

cortices, in agreement with other neuroimaging studies in younger samples [25-27]. However, when the best indicators of aMCI were examined in the young old and oldest old age groups respectively, distinct MRI signatures were noted, i.e., the frontal-striatal (superior frontal cortex and putamen) and temporoparietal (parahippocampus and precuneus) networks in the young old, and hippocampus, and pars triangularis and temporal polar cortices in the oldest old population, even though the effect size is moderate.

In the oldest old, MRI markers of aMCI were again found in the frontotemporal other than the temporoparietal regions, in concordance with the findings in Chapter 4. Compared to the overall cortex, hippocampal atrophy on MRI appears to be an earlier event associated cognitive impairment; but it is not specific to AD pathology at this age [12, 21]. On autopsy examinations, those with cognitive impairment but no dementia were found to be indistinguishable from cognitively normal individuals, with the use of AD pathology, cerebral vascular disease, hippocampus sclerosis, and synaptic loss as pathological markers [28]. The study in Chapter 5 is the first that has explored structural MRI markers of aMCI in the oldest old. The hippocampus, and pars triangularis and temporal polar cortices appeared to be affected in the prodromal stage of clinical dementia; MRI-derived measures of these regions could, therefore, be used to assist in early diagnosis and disease monitoring in the oldest old population.

6.4 Vulnerability and "resilience" in the oldest old

The oldest old is a population with general vulnerability for cognitive impairment; but for some individuals, they present with considerable brain resilience to resist dementia and compensate the underlying neuropathologies.

In Chapter 2, the rates of prevalence and incidence of dementia in representative samples continued to increase with advancing age, suggesting an increased risk of dementia in the oldest old. In Chapter 3, a linear negative relationship of age with MRI-derived measures of grey matter into 10^{th} and 11^{th} decades of life was seen, in non-demented ageing, with the greatest effect in hippocampus and temporal-posterior cortices. Further in Chapters 4 and 5, small hippocampus and thin cortex on select cortical regions were related to both prodromal and clinical dementia at advanced ages. Together, these neuroimaging findings suggest that age-related brain loss predisposes the oldest old to substantial risks of cognitive decline and dementia, supporting the notion of cognitive vulnerability from a neuroimaging standpoint.

In spite of the general vulnerability, those oldest old who remained dementia-free were found to have relatively "preserved" frontal-temporal cortices and select subcortical nuclei (hippocampus, thalamus and amygdala), and this was a consistent finding across Chapters 3, 4 and 5. The medial temporal lobe was prominently affected in both non-demented and dementia-associated ageing in the oldest old, but to a lesser degree in those with better cognitive functioning. This is in agreement with studies in the young old [6]. Since the temporal atrophy is related to varying neurodegenerations that are common at advanced ages [12, 22], its relative "preservation" may indicate less severe neuropathologies within the episodic memory system, leaving more neuronal resources to maintain the cognitive functioning.

Moreover, the prefrontal cortex and select subcortical nuclei are of particular interest in the oldest old. The inferior frontal gyrus, rostral middle frontal and lateral orbitofrontal cortices were considerably less affected in non-demented ageing in the 90-plus (Chapter 3). Thinner prefrontal cortex was related to dementia status at 95 years (test-wise $p <$

0.05) (Chapter 4), and part of the inferior frontal gyrus (pas triangularis) was found to be a marker of aMCI in the 85-plus population (Chapter 5). Similarly, the sparing of a few subcortical structures (such as amygdala and thalamus) was exclusively found in non-demented oldest old, but not the demented ones (Chapter 3 and 4). Together, these suggest that the "preservation" of select frontal-subcortical grey matter is an MRI feature of successful cognitive ageing. Prefrontal cortex is thought to be a key substrate of brain resilience in coping with abundant neuropathologies, as shown by autopsy examination [29], as well as structural [30], functional [31] and metabolic [32] neuroimaging studies in the young old. The frontal-subcortical circuit has been widely implicated in executive function and working memory, both of which interact with memory skills for engaging efficiently in cognitive tasks [33-36]. Therefore, these "preserved" frontal-subcortical structures may reflect compensatory mechanisms to maintain a reasonable cognitive functioning in successful cognitive ageing, despite possible underlying neuropathologies.

6.5 Limitations of this research

Several limitations of this thesis deserve attention. First, it is cross-sectional and therefore cannot account for baseline cognitive function and brain volumetrics. The reference to "atrophy" or "preservation" is therefore speculative as it assumes a comparison to a previous level. Yet there are practical difficulties in conducting follow-ups over an extended period of time, and the selective attrition is high at advanced age. Cross-sectional design seems therefore to be a time- and cost-effective alternative for sampling adequate individuals across several age decades.

Second, some sampling bias was inevitable. Although both the SCS and MAS were designed to recruit a representative cohort of the population, participants who agreed to

undergo a research MRI were generally more educated and in better physical health and cognitive functioning than those who declined MRI. This became more evident with advancing age, making the very old participants more "health" biased and less representative of the population. This was controlled statistically for possible confounders in the analyses.

Third, this thesis included participants from two population-based studies (SCS and MAS). While there were substantial similarities in geographic areas and methodologies between the two studies, some differences in the neuropsychological batteries were inevitable as the standard 3-hour assessment for the young old was generally poorly tolerated by the oldest old. The differentiation between cognitive categories in the oldest old individuals became therefore more difficult. This was overcome by only including participants with sufficient data for classification to proceed, taking account of other factors that may interfere with cognitive performance such as sensory impairment and physical frailty, and statistically examining for cohort effects across the two studies. The same diagnosis criteria were applied in both the young old and oldest old and the cognitive categories were determined by expert consensus conference.

Fourth, the sample sizes of dementia and MCI participants were moderate. Although the statistical power was adequate in addressing the primary research hypotheses, the sample size did not allow for more detailed analyses of the interactions between different MRI markers as discussed in Chapters 4 and 5.

Fifth, the FreeSurfer and FSL neuroimaging tools suffer from some limitations. Although both tools are regarded highly reliable [37, 38], the accuracy of the thickness estimation by FreeSurfer is known to vary slightly across the cortical mantle [39], and the FSL does tend to overestimate the subcortical nuclei, such as hippocampus volume

[40]. In addition, application of these neuroimaging techniques in the very old did result in more errors than that seen in younger participants. These were examined by reliability analyses of the neuroimaging data (details described in Chapter 3), and were controlled by rigorous quality inspection and manual editing after the automatic imaging processing, by the candidate who had been trained in neuroanatomy and neuroimaging.

6.6 Future directions

The findings and limitations of this thesis suggest several areas for future research in the oldest old population. First, longitudinal studies with multiple waves of clinical and neuroimaging data are warranted, to account for individual variability in trajectories of cognitive and brain ageing and the varying speed of lesion development.

Second, additional neuroimaging features need to be examined in larger samples of the oldest old. Amyloid and tau imaging could provide additional information on the progress of AD pathology and its relationship with cognitive trajectory at advanced age. Including other vascular markers, such as micro-bleeds (susceptibility weighted imaging) and micro-infarcts (7T MRI), would provide a more comprehensive assessment on brain vascular injuries. Microstructures of the white matter (diffusion tensor imaging) also warrant investigations, which might better correlate with the cognitive function.

Third, brain resilience is common in those oldest old. Therefore, brain connectivity, structural and functional, may serve as measureable neuroimaging substrates of brain reserve and cognitive reserve, so as to offer insight into the compensation mechanisms at advanced age.

Fourth, successful cognitive ageing reflects accumulated effects of lifetime exposure to genetic and environmental factors. Growing evidence has suggested that the effects of genetic variations on brain structure and cognitive function increase as people age [41, 42], yet the "blueprint" of the advantageous genes in successful cognitive ageing remains largely unexplored. A better understanding of the genomic, proteomic and epigenomic factors that protect against cognitive impairment in the face of neuropathologies will help to develop more targeted interventions to prevent dementia [43].

Fifth, increasing reports suggests that the structure and function of the brain could be improved by behavioural factors, such as cognitive and physical exercise in late life [44-47]. It is not clear whether these behavioural modifiers are associated with successful cognitive ageing into the 10^{th} and 11^{th} decade of life. A broader range of potential therapeutic targets, taking account of behavioural and social mechanisms, might be warranted to promote successful cognitive ageing.

6.7 Conclusions

This thesis is the first, to my knowledge, to systematically investigate the structural MRI profiles of those oldest old with and without cognitive impairment. A number of prominent findings, listed as follows, contribute to knowledge in the fields of ageing and dementia.

1. The structural MRI profile of non-demented individuals after the age 90 was characterised by a "temporal-posterior" pattern of grey matter loss and extensive accumulation of WMHs, in particular the deep WMHs. This topographic distribution of grey matter loss was different from the "frontal-temporal" pattern in normal ageing and the "temporal-parietal" pattern seen in Alzheimer's disease.

2. The association between structural MRI and clinical dementia was strongest for the hippocampal volume and mean cortical thickness, in both the young old and oldest old. Vascular markers, WMHs and brain infarcts, were indicators of clinical dementia at 80, but not at 95 years. When both atrophy indices and vascular markers were accounted for by an MRI composite pathology index, the association between the later and clinical dementia significantly attenuated at more advanced ages, suggesting potential brain resilience in those who remained dementia-free in exceptional longevity.
3. Structural MRI distinguished aMCI, but not naMCI, from cognitively normal individuals in the sample used in this thesis. MRI markers that best distinguished aMCI from normal individuals differed in those < 85 and ≥ 85 years. The "preservation" of select frontal and temporal structures in cognitively normal individuals after the age 85 is suggestive of possible compensatory mechanisms to protect against cognitive decline and cope with possible underlying neuropathologies.

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