Morphological Analysis of Cerebral Cortex based on Magnetic Resonance Imaging in the Elderly

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by

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CERTIFICATE OF AUTHORSHIP/ORIGINALITY

I certify that the work in this thesis has not previously been submitted for a degree nor has it been submitted as part of requirements for a degree except as fully acknowledged with the text.

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ABSTRACT

Aging is generally associated with cognitive decline and the increased probability of a specific disease, such as Alzheimer's disease (AD). Despite intensive research into the aging brain, the mechanisms underpinning cognitive aging and the risk factors for AD still remain unknown. Magnetic resonance imaging (MRI) has been used as a valuable non-invasive technique for detecting changes within the brain in vivo. Several researchers have already applied computer-based brain morphometry techniques based on MRI. Most previous studies focus on measuring cortical thickness or brain volume, while few studies examine features of the cortical sulci, which embed at least two distinct sources of genetic influences. The goals of this dissertation are to use novel computer-based brain morphometry techniques in T1-weighted scans in the elderly to reveal cortical sulcal variability with aging, cognitive decline, and earlier-stage AD, in order to assist with the prevention of cognitive disorders. There are three sub-projects within this dissertation. Firstly, using automated methods, we measured the global sulcal indices (g-SIs) of both cerebral hemispheres and the average sulcal span in five prominent sulci from a large community cohort of 319 non-demented individuals aged 70–90 years. Our findings suggest that both age and sex contribute to significant cortical gyrification differences and variations in the elderly. The first study establishes a reference for future studies of age-related brain changes and neurodegenerative diseases in the elderly. Secondly, we examined the relationship between cortical features and cognitive function in the same sample. To our knowledge, this is the first study to examine three-dimensional cortical sulcal patterns in community-dwelling elderly with

multiple cognitive domains. The results showed the cognitive performances were correlated with sulcal features but not with cortical thickness. The findings suggest that regionally specific sulcal morphology is associated with cognitive function in elderly individuals. In the third study, we investigated sulcal morphology and cortical thickness in earlier-stage AD. The results suggest that abnormalities of the cortical sulci are characteristic of patients with even very mild AD, and could facilitate early diagnosis of this condition. In summary, we found changes in brain structure, especially the cortical surface, are associated with aging, cognitive decline, and AD. The novel sulci features may contribute to building biomarkers of cognitive decline and AD, and ultimately to assisting with the prevention of cognitive disorders.

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THESIS-RELATED PUBLICATIONS

This thesis is based on the following original publications:

Journal

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Tao Liu; Wen Wei; Wanlin Zhu; Nicole A Kochan; Julian N Trollor; Simone Reppermund; Jesse S Jin; Suhuai Luo; Henry Brodaty; Perminder S Sachdev. The relationship between cortical sulcal variability and cognitive performance in the elderly. *NeuroImage* 2011; 56(3):865-873

Tao Liu; Wei Wen; Wanlin Zhu; Julian Trollor; Simone Reppermund; John Crawford; Jesse S Jin; Suhuai Luo; Henry Brodaty; Perminder Sachdev. The effects of age and sex on cortical sulci in the elderly. *NeuroImage* 2010;51(1):19-27

Conference

Tao Liu; Wei Wen; Wanlin Zhu; Jesse S Jin; Suhuai Luo; Perminder Sachdev. The influence of memory on cortical correlations in the elderly. *15th Annual Conference of the Organization for Human Brain Mapping*, June, 2009, San Francisco, USA.

Tao Liu; Feng Shi; Yuan Zhou; Wanlin Zhu; Lei Lin; Jesse Sheng Jin; Tianzi Jiang, Suhuai Luo; Mira Park; Paul Rasser; Ulrich Andreas Schall. Morphological abnormalities of the cerebral cortical thickness in schizophrenia. *14th Annual Conference of the Organization for Human Brain Mapping*, June, 2008, Melbourne, Australia.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AC	Anterior Commissure
AD	Alzheimer's disease
ADNI	Alzheimer's Disease Neuroimaging Initiative
APOE	Apolipoprotein E
ANOVA	Analysis of Variance
BET	Brain Extraction Tool
CDR	Clinical Dementia Rating Scale
CSF	Cerebral Spinal Fluid
DTI	Diffusion tensor imaging
FDR	False discovery rate
fMRI	Functional Magnetic Resonance Imaging
GSI	Global Sulcal Index
GM	Gray Matter
ICV	Intracranial Volume
LH	Left Hemisphere
MANOVA	Multivariate Analysis of Variance
MCI	Mild Cognitive Impairment
MMSE	Mini Mental Status Exam
MRI	Magnetic Resonance Imaging
NC	Normal Control
OASIS	Open Access Serier of Imaging Studies
PC	Posterior Commissure
PET	Positron Emission Topography
RH	Right Hemisphere
ROI	Region of Interest
SD	Standard deviation
SI	Sulcal Index
sMRI	Structural Magnetic Resonance Imaging
SPM	Statistical parametric mapping
SS	Sulcal Span
VBM	Voxel Based Morphometry
WM	White Matter

CHAPTER 1: OVERVIEW

This chapter provides a high-level overview of the proposed research topic, morphological analysis of cerebral cortex based on magnetic resonance imaging in the elderly. It begins with a description of the background and the motivation of the research. Then, it summarizes the goals of the study.

1.1. Background

The worldwide elderly population is rapidly increasing. Between 30 June 1990 and 30 June 2010, the percentage of individuals over 65 in Australia has increased from 11.1% to 13.6%, and those over 85 has more than doubled from 0.9% of the population at 30 June 1990 to 1.8% of the total population at 30 June 2010 (Australian Bureau of Statistics, 2010). The growth of the aging population is projected to accelerate in the coming decades. According to the Australian Bureau of Statistics projections, the proportion of people aged 65 years and over is projected to increase by 2.8 % from 13.6% to 16.4% between 2010 and 2015.

Aging is generally associated with physiological stress and increased probability of specific diseases, such as cardiovascular disease, hypertension and Alzheimer's disease. A significant percentage of the elderly population experience cognitive impairment,

which significantly lowers the individual's quality of life (Graham et al., 1997). It is also known that aging accompanied by cognitive decline is the primary risk factor for dementia such as Alzheimer's disease (AD) (Yankner et al., 2008). AD has a profound effect on the sufferer, the family and on society. The care and treatment of the dementia or other aging-associated diseases will create a huge economic burden (Wimo et al., 2006). Therefore, prevention of dementia is a great challenge for current scientists.

Magnetic resonance imaging (MRI) has been used as a useful non-invasive technique to detect changes within the brain in vivo. Based on MRI, the technique of brain morphometry on living brains has led to great advances in neuroscience research recently (Bang-Bon Koo and Kim, 2010). Brain morphometry is a technique involving the quantification of structural characteristics of the brain, and changes thereof, in individual or group subjects (Bang-Bon Koo and Kim, 2010). The technique can be performed across different scales, from the axonal morphology of a single neuron to its whole ensemble (Bang-Bon Koo and Kim, 2010; van Pelt et al., 2001). The improving sophistication of MRI permits brain structures to be visualized in vivo in exquisite detail with fine soft-tissue contrasts resolution (Bang-Bon Koo and Kim, 2010). Such detailed structural imaging allows us to quantify anatomical features of the cerebral structures such as the volume, cortical thickness and shape, and to derive more specific information, such as sulcal span, gyrification and sulcal index in living subjects.

Voxel-based morphometry (VBM), which is used to measure cortical density and volume, has been widely applied to the study of brain morphometry (Ashburner, 2009) during the past 10 years. More recently, when cerebral cortex draws concern, cortical thickness has become a choice for elevating cortical morphology because of a simpler interpretation than the results obtained by VBM (Ashburner, 2009). The cerebral cortex is able to be investigated by cortical thickness and surface area; both of the two measures embed at least two distinct sources of genetic influences (Panizzon et al., 2009). In contrast to the study of cortical thickness, few studies examine features of the cortical sulci and cortical folding, although the cortical surface area characterizes the variability of the cortex.

1.2. Objectives

In order to prevent dementia in elderly, current neuroscientists are keen to overcome two challenges: 1) to understand the mechanisms underpinning cognitive impairment and the disturbing progression from normal aging to dementia in elderly aged 60+ years old, and 2) to identify modifiable risk factors for aging-associated diseases, such as AD.

Therefore, the initial motivation of this dissertation is to use computer-based brain morphometry techniques to assist neuroscientists to overcome the above two challenges. The present study, therefore, has developed into three subprojects corresponding to the three targets: 1) to better understand the age-related cortical changes and sex difference

in elderly, 2) to characterize the relationships between cognitive functions and the cerebral cortex, and 3) to investigate the abnormalities of the cortex in elderly-stage AD for facilitating the early diagnosis of this condition. Based on the MRI technique, the changes of cerebral cortex are reflected by the cortical thickness and the cortical sulci. Most previous studies have focused on the traditional measurement, i.e. cortical thickness, grey matter (GM) density and GM volume; this research mainly concentrate on the novel indices of the cortical sulci and the cortical folding although we also compute the traditional measures in the subprojects.

1.3. Description of chapters

Including the current chapter, this dissertation consists of 7 chapters and a bibliography.

- Chapter 2 gives a brief background on the basic principle of aging brain, cognitive function and AD, and the related findings using neuroimaging technique.

- Chapter 3 presents the proposed methodologies which are performed on the project. The proposed methodologies include neuropsychological assessments; measuring cortical sulci and cortical thickness using neuroimaging technique.

- Chapter 4 aims to achieve the first target, which is to understand the age-related cortical changes and sex difference in the elderly. The first study establishes a reference for studies of cognition-related brain changes (related to the second target) and neurodegenerative diseases (related to the third target) in the elderly.

4

- Chapter 5 aims to achieve the second target, which is to characterize the relationships between cognitive functions and cortex include the cortical sulci and cortical thickness in elderly. The second study also relates and set up a background to the third subproject, because AD is characterized by an insidious onset of cognitive decline.

- Chapter 6 aims to achieve the third target, which is to investigate cerebral cortex in early-stage AD in the elderly. Understanding the brain changes associated with AD at its mildest stage may facilitate the development of early interventions for this debilitating condition.

CHAPTER 2: BACKGROUND

This chapter reviews related work, including the basic principle of aging, cognitive function and AD; and the related findings using neuroimaging in previous studies.

2.1. Aging

Age is a major risk factor for most common neurodegenerative diseases, including Alzheimer's disease, cerebrovascular disease, Parkinson's disease and Lou Gehrig's disease. Research suggests that the aging process is associated with several structural, chemical, and functional changes in the brain as well as a host of neurocognitive changes.

Post-mortem studies

Autopsy studies have reported consistent age-related reductions in brain weight, brain volume and cortical volume (Creasey and Rapoport, 1985; Luft et al., 1980; Miller et al., 1980; Terry et al., 1987). Dekaban et al.(1978) indicated that brain weight and size were reduced in elderly human subjects; by 86 years, mean brain weight had decreased by about 11% of its maximum at about 19 years of age (Dekaban, 1978). Another post-mortem study found that the hemispheric volume remained roughly constant between the ages of 20 and 50 years (558 ml for men, 474 ml for women), but fell by around 2% per decade after 50 years of age (Miller et al., 1980). The inspection of gross anatomy of the brain samples revealed diminished cortical volume in elder adults and the results

indicated that there was some neuronal loss with age (Terry et al., 1987). The limitation of post-mortem studies are that the neuropathologic measures are subject to sources of error such as selection bias, technical and fixation artifacts, and the influence of pre-morbid illness and cause of death (Coffey et al., 1992).

Neuroimaging studies

Neuroimaging techniques avoid many of problems in post-mortem studies and provide an opportunity to investigate brain morphology in vivo and to qualify brain changes with aging. Courchesne et al.(2000) first examined quantitative changes of normal brain in life span from early childhood to late adulthood using MRI based on 116 subjects aged 19 months to 80 years (Courchesne et al., 2000). They found grey matter volume increased 13% from early to later (6–9 years) childhood; then the grey matter volume increased more slowly and reached a plateau in the 4th decade; thereafter, it decreased by 13% in the oldest volunteers (Courchesne et al., 2000). Furthermore, in a recent study, it has been suggested that the total cerebral volume declined at an annual rate of 0.4% per year in elderly subjects aged between 55 and 86 years (Chee et al., 2009; Jack et al., 2005). It is noteworthy that the rate of atrophy is lower in the cohorts containing young adults than in the cohorts only containing elderly subjects. A study containing subjects aged between 20 and 80 years found the total cerebral volume declined by 0.22% per year with accelerated decline in advanced aging (Fotenos et al., 2008). Besides the finding in total cerebral volume, it has been shown that with age, there is a reduction of gray matter (GM) and white matter (WM) volumes (Raz et al., 2005), and

the GM/WM ratio is also reduced (Courchesne et al., 2000), while the volume of cerebrospinal fluid (CSF) increases with age (Good et al., 2001). Using measures such as regional brain volume, cortical thickness and gray matter density, it has been reported that age-related cortical atrophy is most frequently observed in the frontal (Coffey et al., 1992; Seo et al., 2009; Sowell et al., 2007) and temporal lobes (Coffey et al., 1992; Raz et al., 2005; Sowell et al., 2003). Using manual tracings of cortical regions, Raz et al (1997) reported the greatest age-related reduction in volume in the superior frontal and dorsolateral prefrontal cortices. The greater loss in the multimodal regions was supported by the work of Sowell et al (2003) who used GM density as an indicator of GM thickness.

2.2. Cognitive function

Cognitive function can be defined as the mental process that involves symbolic operations eg, attention, memory, perception, language and executive function. Attention is the cognitive process of focusing on one aspect of the environment while ignoring others; memory indicates an ability to encode, store, and retrieve information and experiences; perception refers to the process of achieving awareness or understanding of the environment by organising and interpreting sensory information; executive function is the process of controlling and managing things, including planning, working memory, attention, problem solving, verbal reasoning, inhibition, mental flexibility, multi-tasking, initiation and monitoring of actions (Chan et al., 2008). There are also several measures to evaluate cognitive function, such as processing

speed-one of the measures of cognitive efficiency, which is involved with the ability to fluently perform cognitive tasks that required high mental efficiency. The basic or sophisticated cognitive function of humans is able to be investigated by a series of cognitive tasks that require active cognitive effort. The neuropsychological assessments, such as Digit Symbol-Coding task (Wechsler, 1997a) and Logical Memory stories A (Wechsler, 1997b) have been widely used in fundamental research and clinical diagnosis.

Attempts to associate brain structure with cognitive function have a long history, going back to the time of phrenology. Recent investigations have used advanced statistical techniques such as regional brain volumetrics or VBM to examine the relationship. Positive correlations between brain structure and cognitive functions have been found, such as processing speed (Kochunov et al., 2010; Tisserand et al., 2000), executive function (Newman et al., 2007) and memory (Tisserand et al., 2000) in cognitively healthy adults. However, the studies have not always been consistent, and some surprising negative correlations have been reported, such as better memory being associated with smaller hippocampal volumes in healthy adults in one study (Van Petten, 2004). Furthermore, a review of the literature on structure-function correlations in aging suggested that "the magnitude of the observed associations is modest" (Raz and Rodrigue, 2006).

2.3. Alzheimer's disease

Alzheimer's disease (AD) is a progressive degenerative disease that is pathologically comprised of amyloid plaques, neurofibrillary tangles, and neuronal and synaptic loss in neocortical and non-neocortical areas of the brain (Greene, 2010). For the early half of the 1900s, AD was mainly considered as a type of senile dementia; but for the later half of the 1900s it was found that both AD and senile dementia showed typical features that Alzheimer had described in 1907 (Kidd, 1963; Terry, 1963). Currently, it is estimated there are 266,574 people with dementia in Australia in 2011, projected to increase to 553,285 people by 2030, and 942,624 people by 2050 (Australia, 2011). For the purpose of preventing or delaying the progression of this disease, it is necessary to recognize individuals who have a chance of contracting AD earlier than the development of cognitive decline. Mild cognitive impairment (MCI) is considered to be an early, or transitional, stage where individuals have an increased risk of converting to a dementia state, and has received intensive attention in the exploration of detecting individuals at risk for developing AD (Greene, 2010).

More recently, the neuroanatomic abnormalities of individuals with AD in vivo have been quantitatively explored in neuroimaging study. MRI-based investigations have utilized volumetric measures of either regions of interest (ROIs) (He et al., 2007; Jack et al., 2004; Shi et al., 2009; Whitwell et al., 2007) or the whole brain (Fotenos et al., 2005; Sluimer et al., 2008), VBM (Chetelat et al., 2005; Hamalainen et al., 2007; Karas

et al., 2003; Li et al., 2008), and cortical thickness (Dickerson et al., 2009; Im et al., 2008b). Across these studies, AD has often been associated with atrophy or cortical thinning in a number of brain regions, including frontal (Hamalainen et al., 2007; Whitwell et al., 2007), temporal (Hamalainen et al., 2007; Whitwell et al., 2007), parietal (Im et al., 2008b; Whitwell et al., 2007) and hippocampal (Chetelat et al., 2005; Jack et al., 2004; Shi et al., 2009).

CHAPTER 3: METHODOLOGY

This chapter gives an overview of the proposed methodology in this thesis, including the neuropsychological assessments, the approach for measuring the features of cortical sulci and cortical thickness.

3.1. Neuropsychological assessments

Assessing cognitive function

In this study, a comprehensive neuropsychological test battery was administered by trained research psychologists. Twelve tests were administered that measured five cognitive domains: processing speed, memory, language, visuospatial and executive function.

Processing Speed

The processing speed domain was assessed by the WAIS - III Digit Symbol - Coding (Wechsler, 1997a) and the Trail Making Test part A (TMT A) (Reitan, 1985). Both tests involve visual search and motor speed skills. In Digit-Symbol Coding test, first pairs of digits and symbols are shown to the participant; then the participants are asked to write down the correct substitution of symbols listed on the test paper. TMT A consists of 25 circles distributed over a sheet of paper. TMT A instructs the participant

to draw lines to connect the numbers in numerical order as fast as possible using a pencil.

Memory

Assessment of memory in our study included: Logical Memory story A (Wechsler, 1997b), three measures from the Rey Auditory Verbal Learning Test (RAVLT) (Rey, 1964) — total learning (sum of trials 1–5), short-term delayed recall (trial 6) and long-term delayed recall (trial 7), and the Benton Visual Retention Test — multiple choice version (BVRT) (Benton and Spreen, 1996). Logical memory (LM) is an index of auditory - linguistic memory function; the instruction of LM asks the participants to verbally recollect a passage from a story following auditory presentation in two time intervals. The RAVLT has proven useful in measuring multiple learning and memory functions, including proactive inhibition, retroactive inhibition, immediate and delayed retention, encoding versus retrieval, and susceptibility to interference (Rey, 1964). In the standard RAVLT, participants first listen to a list of 15 unrelated words which was read by an examiner at the rate of one per second; then, they are required to recall the words freely. This procedure is performed five times using the same lists of 15 words. After the fifth recall, the examiner presents a different list of 15 words, performing the procedure only one time and immediately afterwards, asks the participant to recall the initial list of words.

Language

Semantic fluency (Animals) (Spreen and Benton, 1969) and the 30 item Boston Naming Test (BNT) (Kaplan, 2001) are used to assess language function. Semantic fluency entails the generation of words. The participant was required to generate as many animal names from a given category within a pre-set time of 60 seconds. Boston Naming Test (BNT) is a confrontation naming test commonly used in clinics in the examination of children with learning disabilities and the evaluation of brain-injured adults. Participants in BNT are required to verbally name the objects from line drawings.

Visuospatial

Visuospatial skills were assessed using the Block Design task (Wechsler, 1981). The test is required to take blocks that have all white sides, all red sides, and red and white sides and arrange them according to a pattern.

Executive function

Executive function was assessed using the Controlled Oral Word Association Task (COWAT) (Benton, 1967) and Trail Making Test part B (TMT B) (Strauss et al., 2006). The COWAT, a type of phonemic fluency test, is a measure of a person's ability to make verbal association to specified letters (Sumerall et al., 1997). An examiner assigns a letter and asks a participant to verbally generate as many words that begin with that letter as quickly as the participant can.

AD assessment

The evaluation of the progression to AD is able to be examined by several methods of cognitive test, e.g. mini mental state examination (MMSE) (Folstein et al., 1975) and clinical dementia rating (CDR) (Morris, 1993).

MMSE

The MMSE, a brief 30-point questionnaire test, is commonly used to estimate cognitive impairment or cognitive decline in the healthy elderly, and patients with dementia. It is employed to assess five different cognitive functional abilities: orientation, registration, attention and calculation, recall, language and praxis. Table 3.1 lists the range of scores to appraise the cognitive function using MMSE. Although MMSE is probably one of the most widely used standardised cognitive screening tests, it has several limitations (Crum et al., 1993): 1) education levels of participants may influence the scores, 2) it has not enough sensitivity to detect very mild dementia, and 3) abnormalities are not specific to AD.

Table 3.1 Mini Mental State Examination

MMSE Score	24-30	18-23	0-17
Interpretation	Normal	MCI	AD

CDR

CDR was developed at the Memory and Aging Project at the Washington University

School of Medicine in 1979 for the assessment of staging severity of dementia. It was developed primarily to use for staging the progression of AD. A global score of CDR is constructed of scores from six domains, which are: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. This global score is used to estimate and track the stages of dementia and cognitive impairment, in which CDR-0 suggests no cognitive impairment and CDR-3 suggests severe AD (Table 3.2).

Table 3.2 Clinical Dementia Rating

CDR Score	0	0.5	1	2	3
Interpretation	Normal	very mild AD	Mild AD	Moderate AD	severe AD

3.2. Cortical sulci

Cortical sulci were analyzed using the following four steps: i) removal of non-brain tissue; ii) segmentation of brain tissues into GM, WM and CSF; iii) extraction and labeling of the sulci; and iv) measuring the sulcal span and global sulcal indies.

Removal of non-brain tissue

The non-brain tissues such as skull, muscle and fat, etc. were removed by warping a brain mask defined in the standard space back to the raw T1-weighted structural MRI scan. The brain mask for the elderly was obtained from an automated skull-stripping procedure based on SPM5 (Ashburner and Friston, 2000). The SPM5's skull-cleanup tool performed excellently on the elderly brains in our case (98% accuracy rate achieved) .The brain images after non-brain removal consisted of GM, WM and CSF (Figure 3.1-A).

Brain tissue segmentation

A fuzzy-classifier-based, anatomical segmentation method (Mangin et al., 2004; Herndon et al., 1998) was used (Figure 3.1-D) to segment brain tissue into WM, GM and CSF, after applying a field inhomogeneity bias correction (Mangin, 2000). The steps of segmentation were: (a) Raw images were normalized to the standard set of fuzzy classifiers by calculating WM-, GM-, and CSF-weighted images. (b) Tissue-weighted images were segmented using the standard fuzzy classifiers. (c) Voxel volume content was corrected so that no voxel contained more than 100% of two tissues. This step revealed the contour of the cortex. (d) Tissue misclassifications, many of which were obvious in the segmented images of step (c), were corrected. (Herndon et al., 1998).

17

Extraction and identification of the sulci

The BrainVisa (version 3.2.0; http://brainvisa.info/) image processing pipeline extracted hemispheric meshes (Figure 3.1-E) from the boundaries between GM, WM and CSF (Figure 3.1-D). The medial surface of the cortical folds was then calculated using a homotopic erosion technique (Mangin et al., 1995). A crevasse detector was used to reconstruct sulcal structures as the medial surfaces from the two opposing gyral banks (Figure 3.1-F) that spanned the most internal point of sulcal fold to the convex hull of the cortex (Mangin et al., 2004). No spatial normalization was applied to the MRI data to avoid potential bias caused by the sulcus shape deformation induced by the warping process.

Sulcus recognition (labeling) was performed using BV. The BV sulcal identification pipeline (Figure 3.1-G) incorporates a congregation of 500 artificial neural network-based pattern classifiers. Each classifier is tuned to identify a particular feature of the sulcal pattern. These neural networks work collaboratively to identify 56 sulcal structures for each hemisphere. The neural networks were trained on a database of 26 expertly classified brain scans, resulting in a classification with a mean accuracy rate of 76% (Riviere et al., 2002). In our study, perhaps because of higher atrophy in the elderly brains than the trained label BV used, the mean accuracy rate was around 63%.
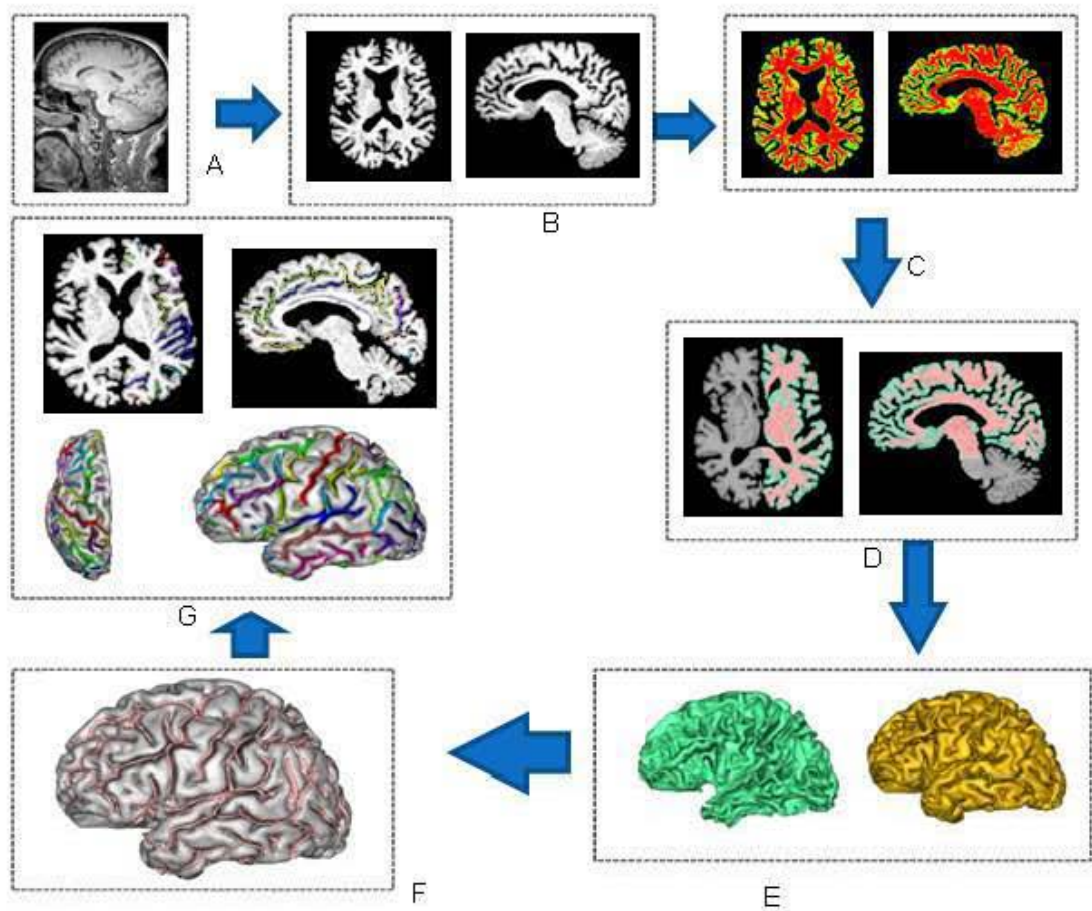
Figure 3.1. Sulcal extraction and identification pipeline consists of (A) raw T1-weighted scan; (B) skull stripping; (C) bias correction; (D) segmentation and computation of White/Gray matter boundary; (E) reconstruction of White/Gray matter mesh; (F) sulci recognition and (G) automated labelling of sulci.

Computation of sulcal features

Global sulcal index

The global sulcal index (g-SI) for each hemisphere was measured as the ratio between the total sulcal area and the outer cortex area (Figure 3.2) (Cachia et al., 2008; Penttila et al., 2009). The total sulcal area was calculated as the sum of the area of all the segmented cortical folds, with the area of each cortical fold being defined as the sum of all the triangle areas defining the fold mesh. The hemispheric outer cortex area was defined as the area of a smooth envelope of the brain mask. The envelope was created by a morphologic closing of the brain mask (Mangin et al., 2004).

A cortex with extensive folding has a large g-SI, whereas a cortex with a low degree of folding has a small g-SI (Figure 3.3). If the outer cortex area is kept as a constant, the g-SI increases by the number and/or area of sulcal folding, and a diminishing of convolutional patterns in the cerebral cortex will result in g-SI converging to zero. This g-SI does not take into account the gray matter intensity and is, therefore, not sensitive to its possible variations. g-SI describes the burying of the cortex and is slightly different from the standard two-dimensional gyrification index as used in some earlier studies (Armstrong et al., 1995; Bonnici et al., 2007). The g-SI used in our study is 3D in nature and is perhaps less sensitive to the cortical thickness and sulcal opening than gyrification index (GI) (Cachia et al., 2008).

We computed g-SI automatically with no manual intervention using BV. Automated g-SI computation is robust and it has recently been applied to the investigation of cortical folding abnormalities in early-onset Schizophrenia (Penttila et al., 2008), intermediate-onset bipolar disorder (Penttila et al., 2009) and newborn infants (Dubois et al., 2008).
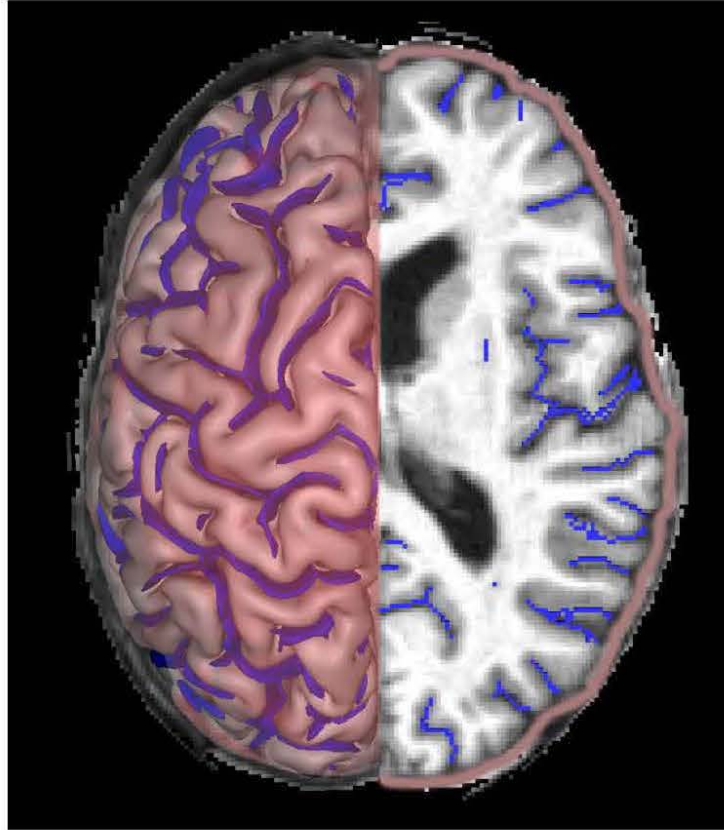
Figure 3.2. The global sulcal index (g-SI) for each hemisphere represents the ratio between the total sulcal area (blue) and the outer cortical area (red).
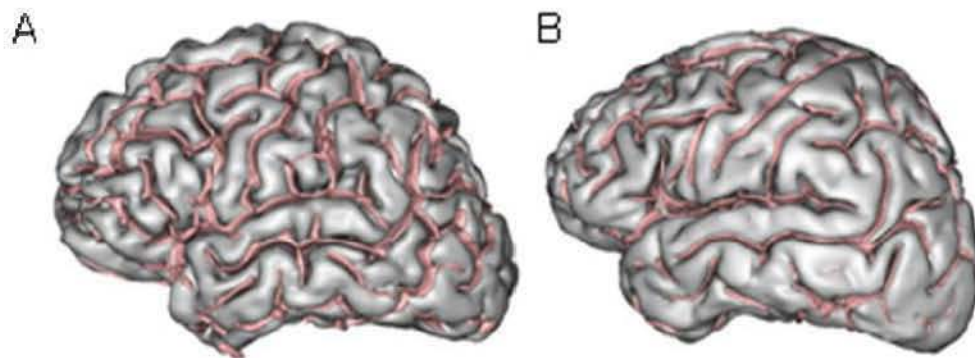
Figure 3.3. Two participants illustrate (A) a high, and (B) a low, overall g-SI.

Sulcal span (SS)

The average sulcal span for an individual sulcal structure was defined as an average 3D distance between opposing gyral banks along the normal projections to the medial sulcal mesh (Figure 3.4) (Kochunov et al., 2008). High-resolution medial sulcal meshes for each sulcus were created by using BV sulcal extraction pipeline. The labeling was firstly performed automatically and then checked visually, and corrected manually, if mislabeled sulci were found. Geometrically, a medial sulcal mesh traverses the sulcal space in the middle of the sulcal span, parallel to the gyral GM borders, and spans the entire sulcal depth. To calculate the sulcal span of individual sulci, the sulcus was identified by using the medial sulcal mesh for each sulcus to seed a 3D region growing algorithm so as to mask the CSF volume within this sulcal structure. To prevent the region-growing from "spilling over" into intersecting sulci, points that were more than

10 mm away from the sulcal skeleton were not considered by the algorithm. The convex hull of the cortical GM ribbon was then used to isolate sulcal space from subarachnoid CSF. The Euclidean distance between two points residing on the gyral GM mesh on either side of the sulcal surface was then taken as the sulcal span. These computations were all implemented in BV and in a sulcal span Plug-In package.

Six primary and secondary fissures, including superior frontal sulcus in frontal lobe, intra-parietal sulcus in parietal lobe, superior temporal sulcus in temporal lobe, cingulate sulcus in limbic area, and interlobar sulci of central sulcus and Sylvian fissure, were selected for investigation from each hemisphere. These sulci were chosen because: (1) they are present in all individuals; (2) they are large and relatively easy to identify to facilitate error detection; and (3) they are located in different cerebral lobes. The extraction and labeling for each scan in its 3D image was visually inspected with care, and the mis-labeled sulci were manually corrected. About 10% (central sulcus) to 40% (superior frontal sulcus) sulci required manual correction in our study. A similar sulcal selection method has recently been applied to the study of cortical morphology in cerebral small vessel diseases (Jouvent et al., 2008) and a normal aging study (Kochunov et al., 2008).
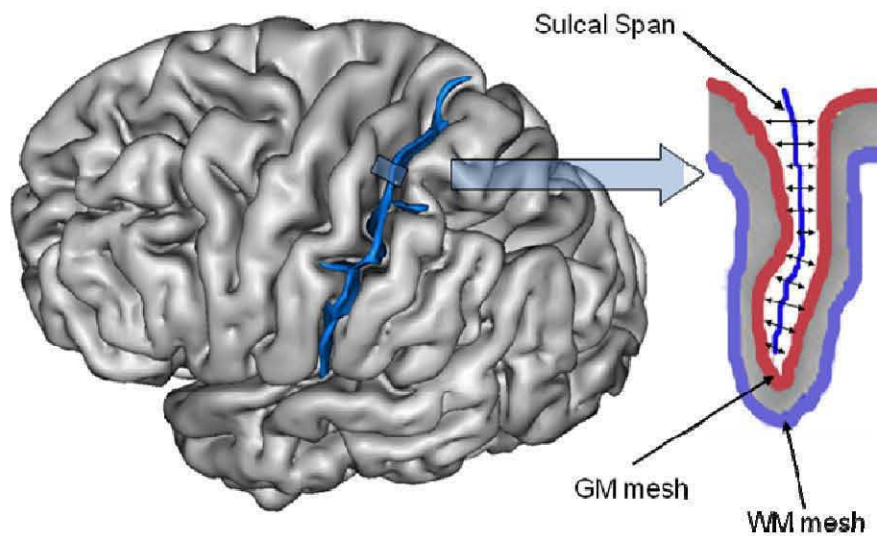
Figure 3.4. The average sulcal width for an individual sulcal structure
is measured as the average width of the intra-sulcal space along the normal projections
to the sulcal mesh. Geometrically, a sulcal mesh transverses the intra-sulcal space in the
middle of the sulcal "width" dimension, parallel to the gyral bank and spans the entire
sulcal "depth".

3.3. Cortical thickness

The MR images were used to calculate thickness of the whole cerebral cortex (Dale et
al., 1999; Fischl et al., 1999), using FreeSurfer software, which had been authenticated
by manual measurements (Kuperberg et al., 2003) and histological anatomy (Rosas et
al., 2002). Based on intensity and neighborhood information, vertices (up to 160 000
per hemisphere) were classified as GM/WM or something else. The procured
segmentations of each subject were visually checked and the obvious defects were

manually corrected. After that, the 'inflated' surfaces were constructed, during which metric distortion was minimized to maintain the original areas as well as distances. The white surfaces were constructed according to the intensity gradients between WM and GM; while the pial surfaces were produced by the intensity contrast between GM and CSF. The distance between the white and pial surfaces defines the thickness at each location of cortex across the entire brain volume. The average regional thickness was calculated for each area of cortex parcellated (Fischl et al., 2004). The atlas used, detailed in (Desikan et al., 2006), included 34 cortical regions of interests in each hemisphere. Freesurfer morphometric procedures have been demonstrated to show good test-retest reliability across scanner manufacturers and across field strengths (Han et al., 2006).

CHAPTER 4: AGE-RELATED CHANGES AND SEX DIFFERENCE IN BRAIN STRUCTURE IN THE ELDERLY

A large number of structural brain studies using magnetic resonance imaging (MRI) have reported age-related cortical changes and sex-difference in brain morphology. Most studies have focused on brain volume or cortical thickness, with relatively few studies of cortical sulcal features, especially in the elderly. In this chapter, we report global sulcal indices (g-SIs) of both cerebral hemispheres and the average sulcal span in six prominent sulci, as observed in T1-weighted scans obtained from a large community cohort of 319 non-demented individuals aged between 70-90 years (mean = 78.06 ± 4.75; male/female = 149/170), using automated methods. Our results showed that for both hemispheres, g-SIs had significant negative correlations with age in both men and women. Using an interactive effect analysis, we found that g-SIs for men declined faster with age than that for women. The widths of all six sulcal spans increased significantly with age, with largest span increase occurring in the superior frontal sulcus. Compared to women, men had significantly wider sulcal spans for all sulci that were examined. Our findings suggest that both age and sex contribute to significant cortical gyrification differences and variations in the elderly. This study establishes a reference for future studies of age-related cortex changes and neurodegenerative diseases in the elderly.

4.1. Introduction

Aging is associated with morphological changes in the brain. These changes have been studied by many investigators using magnetic resonance imaging (MRI). It has been shown that with age, there is a reduction of gray matter (GM) and white matter (WM) volumes (Raz et al., 2005), and the GM/WM ratio is also reduced (Courchesne et al., 2000), while the volume of cerebrospinal fluid (CSF) increases with age (Good et al., 2001). These changes are however not uniform in the cerebral hemisphere. Early histological work showed that multimodal brain regions were more vulnerable to age-related changes than unimodal cortex (Morrison and Hof, 1997, 2007). To some extent this has been substantiated by MRI studies. Using measures such as regional brain volume, cortical thickness and gray matter density, it has been reported that age-related cortical atrophy is most frequently observed in the frontal (Coffey et al., 1992; Seo et al., 2009; Sowell et al., 2007) and temporal lobes (Coffey et al., 1992; Raz et al., 2005; Sowell et al., 2007; Sowell et al., 2003). Using manual tracings of cortical regions, Raz et al (1997) reported the greatest age-related reduction in volume in the superior frontal and dorsolateral prefrontal cortices. The greater loss in the multimodal regions was supported by the work of Sowell et al (2003) who used GM density as an indicator of GM thickness.

A limitation of evaluating brain changes on the basis of GM/WM segmentation is that the contrast between GM and WM decreases with age, due to changes in both T1 relaxation and proton density (Cho et al., 1997; Steen et al., 1995), thereby making the

reliability of the measures of GM and WM volumes age-dependent. To obviate this problem, another approach to examine cortical change has been to measure cortical sulci. It is well-known that cortical sulci widen with age, and this is possibly related to the thinning of the gyri due to reduction in gyral GM and WM (Magnotta et al., 1999; Symonds et al., 1999). Sulcal widening is commonly used by radiologists as a measure of cortical atrophy in the clinical setting. There have been a few systematic studies of changes in cortical sulci with age. Changes are reportedly most prominent in the: central sulcus (Butman and Floeter, 2007; Good et al., 2001; Kochunov et al., 2005), Sylvian fissure (Cykowski et al., 2008; Sowell et al., 2002; Thompson et al., 1998), inferior frontal sulcus (Im et al., 2006; Kochunov et al., 2005; Nordahl et al., 2007) and superior frontal sulcus (Im et al., 2006; Kochunov et al., 2005; Rettmann et al., 2006). The study by Kochunov et al (2005) is noteworthy as they measured sulcal width and depth in 14 sulcal structures per hemisphere in 90 individuals in the age range 20-82 years. They reported that with age, sulci widened by 0.7 mm/decade and became shallower by 0.4 mm/decade, and that multimodal cortical regions were more affected than unimodal regions. While this study covered a broad age range, there were relatively few subjects (n=10) in the age range >70 years.

Sex differences in brain structure have also been reported, with men on average having bigger brains than women at all ages (Blanton et al., 2001; Nopoulos et al., 2000; Thompson et al., 1998; Xu et al., 2000). In a recent study of sulcal and gyral convolutions, it was found that women had greater gyrification in frontal and parietal

regions than men (Luders et al., 2004). Men have been reported to exhibit steeper age-related declines of gray matter volumes in some regions (Curiati et al., 2009; Raz et al., 2004), and the change in sulcal width and depth is faster in men, especially in the temproal collateral and cingulate sulci (Kochunov et al., 2005). However such sex differences of regional gray matter volumes are not consistent across studies (Smith et al., 2007), and sex differences in sulcal morphology have not been examined in the elderly.

In this paper, we report global and regional cortical sulcal morphometry in an elderly sample, with the focus being changes in non-demented community-dwelling individuals in the age range 70-90 years. This age range is of particular importance as cognitive disorders are common at this age, and understanding brain morphological changes that might underlie cognitive deficits is of interest. To our knowledge, there is only one published study on sulcal morphometry in the elderly (Rettmann et al., 2006) with 35 subjects, which demonstrated cross-sectional age-related differences in sulcal depth, local gyrification index and measures of curvature. These subjects were followed up for 4 years and showed a longitudinal decrease in surface area and sulcal depth, and a change in sulcal curvature. Our study is cross-sectional but the sample size is much larger (N=319), enabling us to examine the interaction between age and sex in relation to sulcal morphology. We use automated sulcal analysis software that was based on the MRI contrast between GM and CSF, as this remains stable with age (Kochunov et al., 2005).

4.2. Methods

Subjects

Participants were drawn from the Wave 1 of the Sydney Memory and Aging Study (MAS), a prospective study examining the predictors of cognitive decline in an elderly, non-demented, community-dwelling sample. They were recruited randomly from the electoral rolls of two electorates of Eastern Sydney, Australia. Registration on the electoral roll is compulsory. Participants were excluded from the study if they had been diagnosed as having: dementia, mental retardation, a psychotic disorder including schizophrenia or bipolar disorder, multiple sclerosis, motor neurone disease, active malignancy, and the inability to complete a basic assessment owing to a lack of proficiency in English. At study entry, participants consisted of 1037 individuals aged 70-90 years and 542 (52.3%) had an MRI scan. There were significant differences in sex, English-speaking background, education years, physical health and cognitive test scores between those who were willing to have a MRI scan and those were not ($p <$ 0.05). Participant characteristics associated with being less likely to have an MRI scan included being of female sex, non-English speaking background, having fewer years of education, poorer physical health and lower neuropsychological test scores. During image processing, 223 brain scans had to be excluded due to masking, segmentation or sulcus labeling errors (see below), giving a sample size of 319 subjects.

Image acquisition

We removed 126 scans from the pool of 542 scans (23%) due to segmentation error and the failure to divide the whole brain into left and right hemispheres. A further 97 scans (18%) were removed from the study due to sulcal extraction error. Of the 319 subjects aged 70-90 years (Mean = 78.02, Std = 4.74) included in our study, 170 were scanned using a Philips 3T *Intera* Quasar scanner (Philips Medical Systems, Best, The Netherlands) located at the Prince of Wales Medical Research Institute, Sydney. The remaining 149 subjects were scanned on a Philips 3T *Achieva* Quasar Dual scanner. The replacement of the scanner in 2007 was due to reasons beyond the investigators' control. However as subject recruitment was random, no systematic sampling bias was likely due to the scanner change. Acquisition parameters for both scanners for T1-weighted structural MRI scans were identical, and they were: TR = 6.39 ms, TE = 2.9 ms, flip angle = 8°, matrix size = 256x256, FOV = 256x256x190, and slice thickness = 1 mm with no gap between; yielding 1x1x1 mm^3 isotropic voxels. Participants scanned with the two different scanners were compared on social, demographic and imaging parameters, and there were no significant differences on sex, years of education, and age; GM, WM, CSF volumes and total intracranial cavity volume (ICV) of the whole brain were not significantly different between the scans of participants scanned in two different scanners after controlling for age, education and sex. We analyzed the scans of five healthy participants who were scanned in both scanners within two months, and no significant scanner difference was found. Furthermore, we did not find any significant scanner difference after examining the relationship between age and sulcal measures of

the entire sample of these two scanners separately. Possible scanner effects were examined by using linear regression analysis of these five subjects. Nevertheless, a binary variable of scanner was included in the statistical analysis as an additional covariate to minimize the possible scanner effect.

Measure sulcal features

The procedures of measuring cortical sulcal span and global sulcal index have been described in Chapter 3.2. In brief, the T1 - weighted MRI scans were processed by sulcal extraction and identification pipeline which combined by SPM and Brainvisa software. After the cortical sulci were extracted and identified, we computed the regional cortical sulcal span and global sulcal index in individual.

Due to the higher than expected error rate, we visually checked all the image-processing steps of each scan, and removed those scans that had masking, segmentation or sulcus labeling errors (e.g. cortical ribbon thinning, gyrus or sulcus missing) from the study. As a result, 319 participants with no significant sex difference on age (T = 0.675, p = 0.50), were included for further analysis.

Six primary and secondary fissures, including superior frontal sulcus in frontal lobe, intra-parietal sulcus in parietal lobe, superior temporal sulcus in temporal lobe, cingulate sulcus in limbic area, and interlobar sulci of central sulcus and Sylvian fissure, were selected for investigation from each hemisphere. These sulci were chosen because:

(1) they are present in all individuals; (2) they are large and relatively easy to identify for facilitating error detection; and (3) they are located in different cerebral lobes. The extraction and labeling for each scan in its 3D image was visually inspected with care, and the mislabeled sulci were manually corrected. About 10% to 40% of each sulci required manual correction in our study. A similar sulcal selection method has recently been applied to the study of cortical morphology in cerebral small vessel diseases (Jouvent et al., 2008) and a normal aging study (Kochunov et al., 2008).

Statistical analysis

Four main effects were tested, i.e. age, sex, years of education, and the interaction between age and sex, on the sulcal measures including g-SI and sulcal span using analysis of covariance (ANCOVA) and multivariate analysis of covariance (MANCOVA). Sex was treated as a fixed factor of 2 levels (male and female), hemisphere as a within-subjects factor of 2 levels (left and right), and age and years of education as continuous covariates, in 8 separate general linear models (Tables 4.1 & 4.2). In all the analyses, ICV was used as a continuous covariate to control for individual brain size because the brain size had a significant positive correlation with g-SI ($r = 0.13$, $p = 0.002$) and average sulcal span ($r = 0.10$, $p = 0.020$). This was consistent with previous studies and suggests that greater local clustering of interneuronal connections would be required in a larger brain (Im et al., 2008; Toro et al., 2008). As six sulci were examined, multivariate effects, Wilks's statistic, and corresponding p-values were calculated for the multivariate hypothesis testing for sulcal

span. Linear regression was then used to investigate the relationship between age and sulcal measures by controlling for sex, years of education, hemisphere and ICV. If significant fixed effects (sex or hemisphere) were found in ANCOVAs and MANCOVAs, Bonferroni-corrected *post hoc* comparison tests were used to further examine fixed factor (e.g. sex, hemisphere etc.) contrasts on g-SI and sulcal spans. The interactions between age and sex as well as age and hemisphere in their relationship to g-SI and SS measures were investigated by testing the assumption of homogeneity of regression slopes in ANCOVA or MANCOVA models and using linear regression to investigate the difference in slope. Even though no interaction between hemisphere and age or sex was found, hemisphere was used as a covariate when analyzing other variables such as age and sex.

In order to examine whether there was any significant scanner effect, five healthy participants were scanned in both scanners within two months. Possible scanner effects were examined by using linear regression analysis of these five participants. Figure 4.1 shows the scatter-plots and regression of the sulcal measurement (g-SI and average span) for the two scanners. The effect of scanner was linear on sulcal measures (R^2_{Linear}=0.982, 0.760, 0.841, 0.894, $p < 0.05$ for right and left g-SIs, right and left sulcal spans, respectively). In addition to these five participants, the scanner-related effects for entire sample were analyzed by treating the scanner as a fixed factor of two levels. Their effects were analyzed by using ANCOVA. Figure 4.2 shows: A) the correlations between the right (and left) g-SI and subject's age; B) the correlations

between the right (and left) average sulcal span width and subject's age. We found there were no significant scanner-related effects for the entire sample on g-SI in relation to age ($p = 0.76$), average SS in relation to age ($p = 0.99$), sex effects on g-SI ($p = 0.10$) or sex effects on average SS ($p= 0.60$).
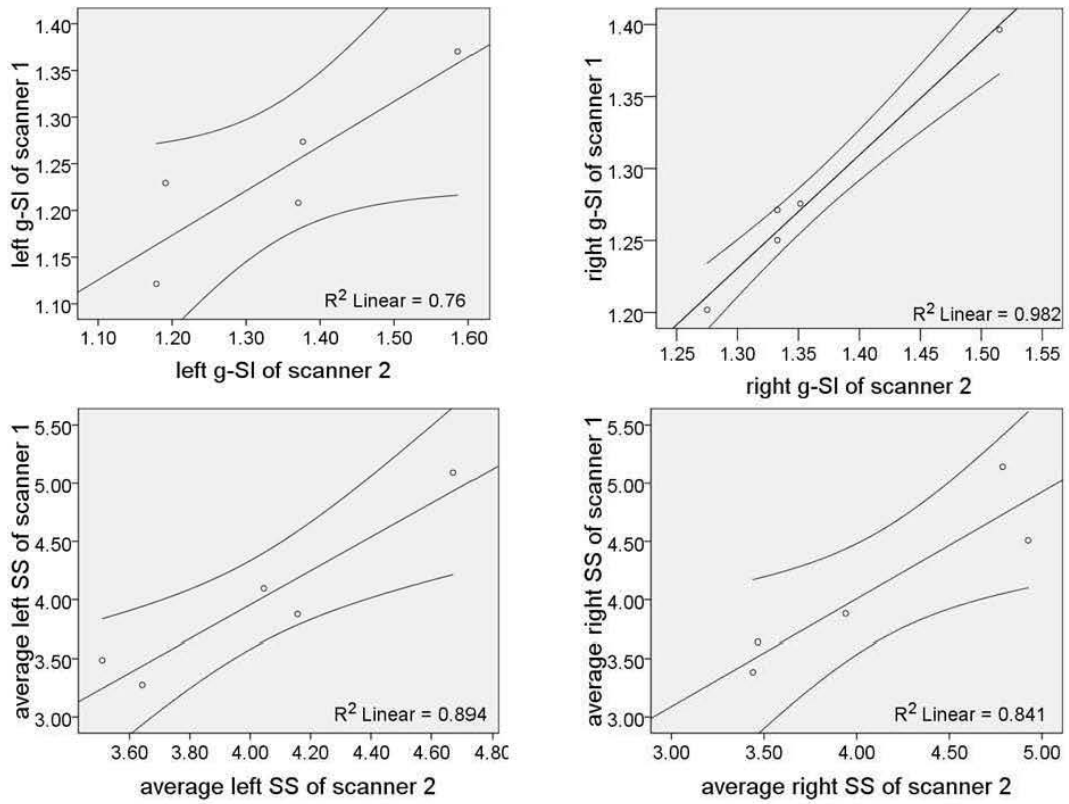
Figure 4.1. Scatterplots of linear regression of the sulcal measures (g-SI and average span) between two scanners of 5 subjects scanned in both scanners. Here average span was calculated as the average of the six sulci that we measured in this study.
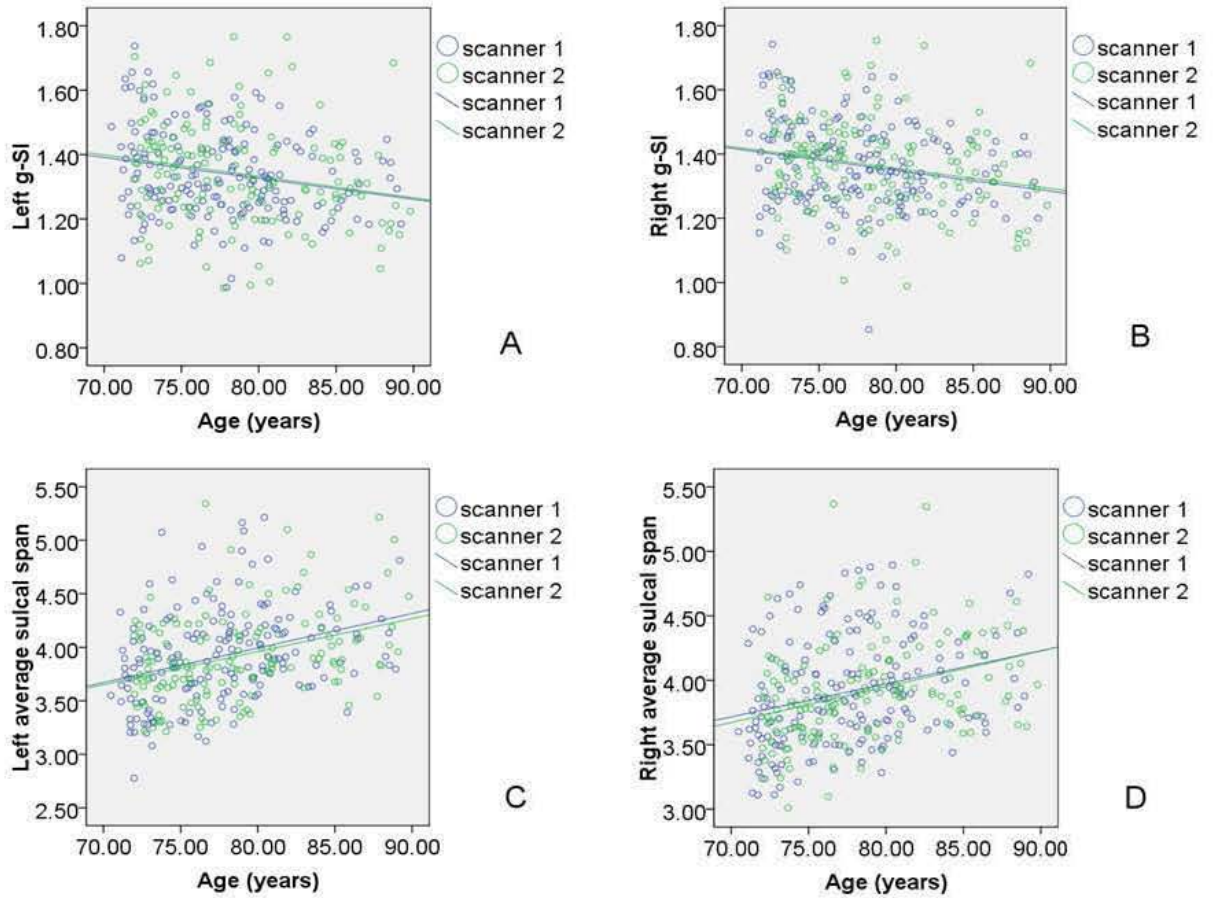
Figure 4.2. Scatterplots and regression lines for g-SI vs. subject's age

(A) & (B) Scatterplots and regression lines for g-SI vs. subject's age of scanner 1 (blue: left T= -2.932, $p = 0.004$; right T = -2.915, $p = 0.004$) and scanner 2 (green: left T = -2.536, $p = 0.012$; right T = -2.725, $p = 0.007$). (C) & (D) Scatterplots and regression lines for average SS vs. subject's age of scanner scanner 1 (blue: left T = 4.575, p <0.001; right T = 3.764, $p < 0.001$) and scanner 2 (green: left T = 4.831, $p < 0.001$; right T = 4.524, $p < 0.001$).

4.3. Results

Global sulcal index

Using ANCOVA, the g-SIs of both hemispheres were found to be significantly associated with age ($F_{(1,631)} = 28.58$, $p < 0.001$), after controlling for sex, years of education, ICV, scanner and hemisphere (Table 4.1). With the same model, g-SI was also found to be significantly related to sex ($F_{(1,631)} = 12.85$, $p < 0.001$) and hemispheres ($F_{(1,631)} = 4.144$, $p < 0.05$). No significant interaction between age and hemisphere on g-SI was found ($F_{(1, 630)} = 0.013$, $p = 0.910$), and no interaction between sex and hemisphere was found in relation to g-SI, suggesting that between-sex difference on g-SI had a similar relationship in both hemispheres. Bonferroni-corrected *post hoc* comparisons of sex effects on g-SI indicated that women had a significantly higher g-SI than men ($T = 3.585$, $p < 0.001$), after controlling for age, education, ICV, scanner and hemisphere. Using the same Bonferroni-corrected *post hoc* comparisons, the g-SI of the left hemisphere was found to be significantly lower than that of the right hemisphere in both men and women ($T = 2.036$, $p < 0.042$), after controlling for age, years of education, ICV and scanner.

Table 4.1: Main effect and age-related interactive effects on global sulcal index

	Source	$F_{(dfM, dfR)}$	p
Main effect	age	28.578 (1, 631)	<0.001 [a]
	sex	12.85 (1, 631)	<0.001 [a]
	education	2.265 (1, 631)	0.133 [a]
	hemisphere	4.144 (1, 631)	<0.050 [a]
Interactive effect	age×sex	6.768 (1, 630)	<0.010 [b]
	age×hemisphere	0.013 (1, 630)	0.910 [c]
	sex×hemisphere	1.150 (1, 630)	0.283 [d]

Table 4.1 reports the results of 4 separate ANCOVA analyses: a). in the first analysis the 4 variables, age, sex, years of education and hemisphere were entered as independent variables in a single block; b). in the second analysis, the interaction between age and sex was entered in the model, with the same 4 control variables; c). in the third analysis, the interaction between age and hemisphere was entered in the model, with the same 4 control variables, and d). in the fourth analysis, the interaction between sex and hemisphere was entered in the model, with the same 4 control variables.

A significant interaction between sex and age was observed (F (1,630) = 6.768, p < 0.01), which suggests that age impacts on global sulcal indices of men and women differently. Linear regression analysis showed that g-SI had a significant negative

relationship with age in both men (beta = -0.300, T = -5.630, $p < 0.001$) and women (beta = -0.122, T = -2.301, $p < 0.05$), but g-SI declined faster in men than in women, i.e. men had a steeper slope (T = 2.60, $p < 0.01$) for g-SI in relation to age than that of women (see Figure 4.3).
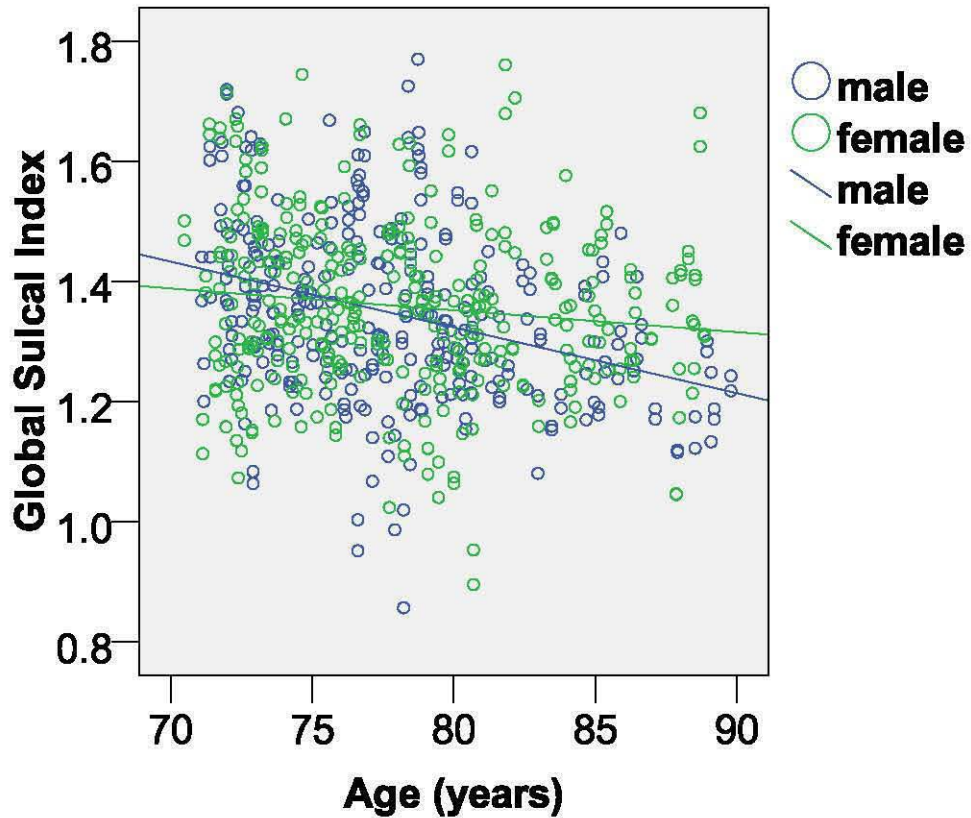
Figure 4.3. Scatterplots and regression lines for global sulcal index vs. subject's age of male (blue) and female (green).

Sulcal span

The relationships of age, sex, years of education and hemisphere with six selected fissures and sulci were examined using MANCOVA. As shown in Table 4.2, age was significantly related to the sulcal spans (Wilks's Lambda = 0.831, $F_{(8,623)}$ = 15.858, p < 0.001) after controlling for sex, years of education, ICV, scanner and hemisphere.

Significant impact was observed on two levels of sulcal span by sex (Wilks's Lambda = 0.954, F (8,623) = 3.779, $p < 0.001$) and hemispheres (Wilks's Lambda = 0.942, F (8,623) = 4.79, $p < 0.001$) after controlling for the other main effects. Unlike g-SI, no significant interactive effect was detected on sulcal span.

Table 4.2. Main effect and age-related interactive effects on sulcal span

	Source	Wilks's Lambda	F	p
Main effect	Age	0.831	15.858	<0.001[a]
	Sex	0.954	3.779	<0.001[a]
	education	0.980	1.579	0.128 [a]
	hemisphere	0.942	4.790	<0.001[a]
Interactive effect	age× sex	0.997	0.220	0.987[b]
	age×hemisphere	0.990	0.781	0.620[c]
	sex ×hemisphere	0.985	1.182	0.307[d]

Table 4.2 reports the results of 4 separate MANCOVA analyses. In all the analyses here, six sulcal span measures were entered in the model as dependent variables: a). in the first analysis, the 4 variables, age, sex, years of education and hemisphere were entered as independent variables; b). the interaction between age and sex was entered in the model, with the same 4 control variables; c). the interaction between age and hemisphere was entered in the model, with the same 4 control variables, and d). the interaction between sex and hemisphere was entered in the model, with the same 4 control variables. Df of F test = (8, 623).

As shown in Table 4.3, the spans of all six sulci became significantly wider with age (p < 0.05 for superior temporal sulcus and p < 0.001 for the other five sulci) after controlling for sex, years of education, ICV, scanner and hemisphere. Using linear regression and partial correlation, it was found that superior frontal sulcus had the highest correlation (r = 0.359, p < 0.001) with age. The span of superior frontal sulcus increased at the highest rate, thereby showing the steepest slope (b = 0.59mm/decade, T = 9.663, p < 0.001) of the six sulci examined. The span of superior temporal sulcus had the lowest correlation with age (r = 0.081, p < 0.05), and the lowest linear increase rate (b = 0.12mm/decade, T = 2.032, p < 0.05).

Table 4.3. The slopes of sulcal span widening with age using linear regression.

Sulcal name	Slope B (std. Error)	*beta*	*T*	*p*
Sylvian fissure	0.044 (0.007)	0.243	6.472	<0.001
Cingulate sulcus	0.032 (0.005)	0.223	5.785	<0.001
Intraparietal sulcus	0.040 (0.006)	0.269	7.020	<0.001
Central sulcus	0.046 (0.005)	0.348	9.339	<0.001
Superior frontal sulcus	0.059 (0.006)	0.360	9.663	<0.001
Superior temporal sulcus	0.012 (0.006)	0.081	2.032	<0.050

Slope B: Unstandardized coefficients (mm/year). Beta: standardized coefficient.

Significant sex differences were found in all six sulci (Table 4.4). Men had significantly wider sulci than women in all regions after controlling for age, years of education, ICV, scanner and hemisphere. The mean male to female difference for sulcal width varied from 0.153 mm for superior temporal sulcus to 0.279 mm for intraparietal sulcus.

Compared with the right hemisphere, the Sylvian fissure (T = 3.919; $p < 0.001$) and superior frontal sulcus (T= 2.790; $p < 0.05$) in the left hemisphere were significantly wider, after controlling for age, sex, years of education, ICV, and scanner.

Table 4.4. inter-gender differences on sulcal span

Sulcal name	Mean difference[a]	std. Error	T	p
Sylvian fissure	0.265	0.079	3.375	<0.001
Cingulate sulcus	0.222	0.064	3.479	<0.001
Intraparietal sulcus	0.279	0.067	4.185	<0.001
Central sulcus	0.217	0.058	3.734	<0.001
Superior frontal sulcus	0.198	0.072	2.754	<0.050
Superior temporal sulcus	0.153	0.071	2.146	<0.050

a: male minus female in mm.

4.4. Discussion

This paper reports the age, sex and hemisphere effects on some sulcal morphological measures, i.e. global sulcal index and sulcal span, of six sulci of both cerebral hemispheres in a cross-sectional study of 319 community-dwelling participants aged between 70-90 years. Both g-SI and sulcal span were found to be correlated with age, sex and hemisphere. In addition, the age-related changes in g-SI were different for men and women, with men having a faster rate of change with age.

Age-related differences

The results showed that g-SIs, which reflected the complexity of sulcal folds, generally decreased with age in both hemispheres irrespective of sex. This finding is in line with

earlier studies which found that the sulci become less curved with aging (Magnotta et al., 1999; Rettmann et al., 2006), and that cortical sulci become wider and shallower with age – as in a cross-sectional study by Kochunov and colleagues (2005) on sulcal morphology with participants ranging from young to early old. The gyrification index (GI) has previously been reported to be independent of the participant's age (Zilles et al, 1988), which is explained by the observation that the widening of the sulci is offset by reduced sulcal depth, so that the ratio between total and exposed cortical surface, which denotes the GI, remains somewhat stable. The difference between the reported age-related stability of the GI and our finding of reduction in g-SIs has two possible explanations: a) previous studies of GI have not examined individuals in the 8th and 9th decades of life; and b) the g-SI and GI are measuring somewhat different properties of the cortex, i.e. the difference is that GI takes into account the entire cortical surface, but g-SI does not include the (top) gyral part of the pial surface, which may make g-SI more sensitive than GI to age-related changes.

Similar to previous studies, this study showed that changes in cortical surface are not uniform over the cerebral hemisphere. While all six sulci became wider with age in the elderly, the superior frontal sulcus showed the steepest slope (increase in width at the rate of 0.59mm/decade) and the largest correlation coefficients with age (beta = 0.36, T = 9.663, $p < 0.001$). This finding of accelerated change in the superior frontal sulcus with age has been previously reported (Kochunov et al., 2005) and is consistent with age-related gray matter atrophy in the superior frontal region as reported in anatomical

studies of aging using different measures such as cortical thickness, cortical density and volume (Fjell et al., 2009; Good et al., 2001; Raz et al., 2004; Raz and Rodrigue, 2006; Smith et al., 2007; Sowell et al., 2001; Xu et al., 2000). It is also consistent with the hypothesis that multimodal cortex is more likely to show morphological change with age (Morrison and Hof, 1997). Our study did not include the full range of cortical sulci so as to comment on changes in unimodal cortical regions. However, the slower rate of widening of the superior temporal sulcus is not inconsistent with this theory. Age-related atrophy has been described in the parietal lobe (Tisserand et al., 2004; Xu et al., 2000), which may explain our finding of "widening" sulcal spans of intraparietal sulcus, and this is consistent with the report by Kochunov et al (2005). Similarly, widening of the cingulate and central sulci is consistent with previous reports, and these sulci are also noted to signify the status of multimodal cortical areas.

Sex differences

The mean g-SI was greater in women than men in both hemispheres (mean (female-male) = 0.05, p < 0.001) after controlling for participants' ICV. The literature on sex differences exploring gyrification indices has been scarce, especially in elderly individuals. This is perhaps because of the difficulty of studying these features in 3D data-sets and the limitations on the postmortem data and non-availability of large sample (Luders et al., 2004; Nopoulos et al., 2000). Using 3D mesh-based measurements of sulcal complexity, it was found that women had greater gyrification than men of 20-30 years of age (Luders et al., 2004). Our study extends this finding to

the older age group. We also found that men had a significantly wider sulcal span in all six sulci than women, after controlling for ICV.

In our study, we found that there was a significant interaction between age and sex on g-SI, with the g-SI of men declining faster with age than that of women. We are not aware of similar findings from previous studies. This finding must be considered in relation to previous studies of cortical gray matter which showed that cortical thinning progressed more rapidly in men than women (Curiati et al., 2009; Magnotta et al., 1999; Raz et al., 2004). Cortical thickness is, however, a different measure from g-SI, the latter being interpreted as a measure of cortical pattern complexity. On the other hand, there was no significant age-related sex difference ($p = 0.987$) in the sulcal span of any of the six sulci that we examined, which suggests that both men and women had their sulci widening at the same rate. Unlike our result, Kochunov et al (2005) reported a larger age-related increase in sulcal width in men, especially in the superior temporal, collateral and cingulate sulci, and this sex difference has been reported in the superior temporal sulcus by other authors as well (Raz et al., 1997; Xu et al., 2000). The differences in the studies are difficult to explain except that our subjects are much older, and it is possible that sex differences in the rate of change become less obvious in the elderly. More work in this area is necessary before a definitive statement can be made.

Hemispheric asymmetry

Global hemispheric asymmetry has been previously reported, with the right hemisphere having a greater brain volume than the left hemisphere in the age range of 20-80 years (Raz et al., 2004). Interestingly, we observed a higher g-SI in the right hemisphere than that in the left hemisphere, which suggests hemispheric asymmetry of gyrus folding. The spans of left Sylvian fissure and superior frontal sulcus were larger than those in the right hemisphere. It was previously reported that Sylvian fissure in the left hemisphere was longer than that in the right hemisphere (Blanton et al., 2001; Thompson et al., 1998), but asymmetry in their width has not been previously reported.

Limitations

First, the use of two scanners to acquire the data had the potential of introducing bias. However, we did not find any significant scanner-related interactive effects, and in fact the inadvertent change in scanner permitted us to examine the data in two parts, with similar findings emerging from both. Second, our conclusions on aging effects are based on the cross-sectional examination of one cohort only. Aging effects are best determined in a longitudinal study to avoid cohort effects. We plan to follow-up our study participants every two years with repeat MRI scans. Third, as our sample was aged 70-90 years we were therefore unable to examine cortical changes through the life-span. Our findings should therefore be restricted to the elderly. Fourth, since our sample only included those who were willing to undergo a MRI scan, the participants

were physically healthier and slightly higher functioning than those who did not have the scans. We consider it unlikely that this would have influenced the salient findings of our study. Fifth, it is not known how sulcal features relate to brain function, and the functional implications of the findings are therefore unclear. We plan to relate sulcal morphology to neuropsychological test performance to determine the significance of these changes. Lastly, we did not examine the determinants of the observed changes in sulcal morphology, which is the subject of further analyses.

4.5. Summary

Our data suggest that the global sulcal index of both hemispheres decrease with age in elderly men and women, with the decline being greater in men. As a person ages, the widths of the spans of the superior sulcal, central, intraparietal, Sylvian, cingulate and superior temporal sulci increase, with largest increase being in the superior frontal sulcus. Our data suggest that both age and sex contribute to cortical gyrification differences and variations in the elderly.

CHAPTER 5: BRAIN STRUCTURE AND COGNITIVE FUNCTION IN THE ELDERLY

The relationship between cognitive functions and brain structure has been of long-standing research interest. Most previous research has attempted to relate cognition to volumes of specific brain structures or thickness of cortical regions, with relatively few studies examining other features such as cortical surface anatomy. In this chapter, we examine the relationship between cortical features, which include cortical sulci and cortical thickness, and cognitive function in a sample (N=316) of community-dwelling subjects aged between 70-90 years (mean = 78.06± 4.75; male/female = 130/186) who had detailed neuropsychological assessments and brain MRI scans. Using automated methods on 3D T1-weighted brain scans, we computed global sulcal indices (g-SIs) of the whole brain, average sulcal spans of five prominent sulci and the average cortical thickness of 34 regions in each hemisphere. The g-SI, which reflects the complexity of sulcal folds across the cerebral hemispheres, showed a significant positive correlation with performance in most cognitive domains including attention/processing speed, memory, language and executive function. Regionally, a negative correlation was found between some cognitive functions and sulcal spans, i.e. poorer cognitive performance was associated with a wider sulcal span. Of the five cognitive domains examined, the performance of processing speed was found to be correlated with the spans of most sulci, with the strongest correlation being with the superior temporal sulcus. Memory

did not show a significant correlation with any individual sulcal index, after correcting for age and sex. Of the five sulci measured, the left superior temporal sulcus showed the highest sensitivity, with significant correlations with performances in all cognitive domains except memory, after controlling for age, sex, years of education and brain size. On the other hand, we cannot found significant correlations between cortical thickness and cognitive scores after multiple comparison corrections. The results suggest that regionally specific sulcal morphology is associated with cognitive function in elderly individuals.

5.1. Introduction

Attempts to relate brain structure to function have a long history, going back to the time of phrenology. Recent investigations have used advanced statistical techniques such as regional brain volumetrics or VBM to examine the relationship. Positive correlations between brain structure and cognitive functions have been found, such as processing speed (Kochunov et al., 2010; Tisserand et al., 2000), executive function (Newman et al., 2007) and memory (Tisserand et al., 2000) in cognitively healthy adults. However, the studies have not always been consistent, and some surprising negative correlations have been reported, such as better memory being associated with smaller hippocampal volumes in healthy adults in one study (Van Petten et al., 2004). Furthermore, a review of the literature on structure-function correlations in aging suggested that "the magnitude of the observed associations is modest" (Raz and Rodrigue, 2006).

Quantification of the morphology of the fold on the cortical surface may be helpful in understanding the relationships between brain structure and function. The pattern of sulcal folds, the principal anatomical landmarks of the human cerebral cortex on the brain surface, exhibits its structural complexity (Welker, 1988) and reflects the underlying connectivity (Van Essen, 1997). In addition, it has been shown that the cortical folding patterns can predict cytoarchitecture beyond what was traditionally expected (Fischl et al., 2008). A review paper suggested that the fold geometry was a macroscopic probe for hidden architectural organization or developmental events (Mangin et al., 2010). Further, previous studies pointed out an advantage of sulcal model-based analysis using the contrast between gray matter (GM) and cerebrospinal fluid (CSF), which unlike the contrast between GM and white matter (WM), remains stable in older subjects (Im et al., 2008; Kochunov et al., 2005). In recent studies of sulcal-based analysis, it was found that folding patterns were modified in psychiatric syndromes and neurological disorders including Alzheimer's disease (Im et al., 2008; Mega et al., 1998), schizophrenia (Cachia et al., 2008) and bipolar disorder (Penttila et al., 2009). Furthermore, morphological difference of sulci had been found in certain professional groups, such as musicians (Li et al., 2009).

The first attempt to quantify the extent of the cortical folding relied on the gyrification index, namely, the ratio of the total pial cortical surface over the perimeter of the brain delineated on two-dimensional slices (Armstrong et al., 1995; Cachia et al., 2008; Luders et al., 2004; Zilles et al., 1988). Recently a new index of sulcal folds, called the

global sulcal index (g-SI), has been computerized as a three-dimensional (3D) version of the gyrification index globally. The g-SI has shown a capacity for being a good biomarker in many studies (Mangin et al., 2010), for example, in detecting abnormalities in early-onset schizophrenia (Penttila J et al., 2008) and intermediate-onset bipolar disorder (Penttila et al., 2008; Penttila et al., 2009). The width of cortical sulci, called the sulcal span, has been proposed as another measure. Several studies have found that the width of cortical sulci expands linearly with aging from early adulthood to old age (Liu et al., 2010; Kochunov et al., 2005; Magnotta et al., 1999). Additionally, developmental abnormalities of cortical sulci in bipolar disorder were observed by examining the width of sulci (Coyle et al., 2006). A recent study also found the average sulcal span in the frontal lobe was negatively associated with processing speed in 38 healthy elderly individuals (Kochunov et al., 2010).

In the present study, we investigate the relationship between cognitive function and global/regional sulcal morphometry based on the cortical surface of non-demented community-dwelling individuals in the age range of 70–90 years by examining the correlations between a range of neuropsychological domains (including attention/processing speed, memory, language, executive function and visuospatial ability) and sulcal features (including global sulcal index and five regional sulcal spans). To our knowledge, this is the first study to examine 3D cortical sulcal patterns in community-dwelling elderly with multiple cognitive domains. In a previous study, we reported that age was correlated with the sulcal pattern (Liu et al., 2010). In

addition, age has been correlated with cognitive functions, and advancing age is generally accompanied by decline in some cognitive functions (O'Sullivan et al., 2001).Therefore, we hypothesized that: i) poorer cognitive function will be associated with wider sulcal span and lower g-SI; ii) the sulcus-performance associations are only partially mediated by age, that is correlations between cognitive functions and sulcal features will be present after correcting for age effects; iii) processing speed, which shows the most consistent age-related decline (Salthouse, 1996; Tisserand et al., 2000), would have the most robust relationship with the global sulcal index and sulcal span; iv) there is regional specificity in the relationships, e.g. executive function with the superior frontal sulcus, language with the superior temporal sulcus, visuospatial function with the intra-parietal sulcus; v) we suspected that memory may not show a relationship with any of the sulci examined as the organs of memory are subcortical and not reflected in these sulci.

5.2. Methods

<u>Subjects</u>

Participants were drawn from Wave 1 of the Sydney Memory and Aging Study (MAS), a prospective study examining the predictors of cognitive decline in an elderly, non-demented, community-dwelling sample. They were recruited randomly from the electoral rolls of two electorates of Eastern Sydney, Australia. Registration on the electoral roll is compulsory for Australian citizens. Participants were excluded from the study if they had been diagnosed as having any of the following: dementia, mental

retardation, a psychotic disorder including schizophrenia or bipolar disorder, multiple sclerosis, motor neurone disease, active malignancy, and the inability to complete a basic assessment owing to a lack of proficiency in English (Sachdev et al., 2010). At study entry, participants were 1037 individuals aged 70-90 years, of whom 542 had an MRI scan. There were significant differences in sex, English-speaking background, education years, physical health and cognitive test scores between those who were willing to have a MRI scan and those who were not ($p < 0.05$). The characteristics associated with those participants who were less likely to have an MRI scan included: being of female sex, non-English speaking background, having fewer years of education, poorer physical health and lower neuropsychological test scores. During image processing, 89 brain scans had to be excluded due to masking, segmentation or sulcus labelling errors (9% segmentation error and 7% sulcal extraction error). After exclusion of participants of non-English speaking background, incomplete information of the neuropsychological tests (removing 137 subjects), 316 subjects with no significant sex difference on age (T = 1.07, p = 0.28), were entered into the study. Some demographic characteristics and mini-mental status examination (MMSE) score (Folstein et al., 1975) of the sample are presented in Table 5.1. It is noted that this was a healthy sample with a mean MMSE score of 28.57/30.

Table 5.1. Demographic characteristics and MMSE score of the sample.

	Total N = 316	Male N = 130	Female N = 186	t value [b]	p value
Age (years)	77.85 (4.55)[a]	77.52 (4.37)	78.08 (4.66)	- 1.07	0.28
Education(years)	11.79 (3.61)	12.67 (4.03)	11.18 (3.16)	3.68	< 0.001
MMSE	28.57 (1.27)	28.41 (1.36)	28.68 (1.20)	-1.81	0.07

a Mean (SD)

b comparison between male and female by two-tailed t test

Image acquisition

Of the 316 subjects included in our study, 194 were scanned using a Philips 3T *Intera* Quasar scanner (Philips Medical Systems) located at the Prince of Wales Medical Research Institute, Sydney. The remaining subjects were scanned on a Philips 3T *Achieva* Quasar Dual scanner. The replacement of the scanner in 2007 was due to reasons beyond the control of the investigators. However, as subject recruitment was random, it was unlikely that any systematic sampling bias was introduced by the scanner change. Acquisition parameters for both scanners for T1-weighted structural MRI scans were identical; they were: TR = 6.39 ms, TE = 2.9 ms, flip angle = 8°, matrix size = 256x256, FOV = 256x256x190, and slice thickness = 1 mm with no gap between; yielding 1x1x1 mm^3 isotropic voxels. Participants scanned with the two different scanners were compared on social, demographic and imaging parameters, and there were no significant differences on sex, years of education, and age; GM, WM,

CSF volumes and total intracranial cavity volume (ICV) of the whole brain were not significantly different between the scans of participants scanned by two different scanners after controlling for age, education and sex. We analyzed the scans of five healthy participants who were scanned on both scanners within two months, and no significant scanner differences were found in their sulcus morphometry (Liu et al., 2010). Furthermore, we did not find any significant scanner difference after examining the relationship between age and sulcal measures of the entire sample of these two scanners separately. Possible scanner effects were examined by using linear regression analysis of these five subjects. Nevertheless, a binary variable of "scanner" was included in the statistical analysis as an additional covariate to minimize the possible scanner effect.

Neuropsychological tests

A comprehensive neuropsychological test battery was administered by trained research psychologists. Twelve tests were administered that measured five cognitive domains (Table 5.2): attention/processing speed, memory, language, visuospatial and executive function. Details of the administration of neuropsychological tests for the participants were described in Chapter 2. Digit Symbol-Coding task (Wechsler, 1997a) and Trail Making Test part A (TMT A) (Strauss, 2006) were used to assess attention/ processing speed. Assessment of memory included: Logical Memory story A (Wechsler, 1997b), three measures from the Rey Auditory Verbal Learning Test (RAVLT) (Rey, 1964) - total learning (sum of trials 1-5), short-term delayed recall (trial 6) and long-term

delayed recall (trial 7), and the Benton Visual Retention Test – multiple choice version

(BVRT) (Benton, 1996). Semantic fluency (Animals) (Spreen, 1969) and the 30 item

Boston Naming Test (BNT) (Kaplan, 2001) was included as measures of language.

Executive function was assessed using the Controlled Oral Word Association Task

(COWAT) (Benton, 1967) and Trail Making Test part B (TMT B) (Strauss, 2006).

Visuospatial skills were assessed using the Block Design task (Wechsler, 1981).

Table 5.2. Cognitive domains and neuropsychological tests used in the current study

Cognitive domain	Neuropsychological Test	N	Mean	SD
Processing Speed	Digit Symbol Coding	316	50.13	12.17
	Trail Making Test A	316	44.7	15.53
Memory	Logical memory (story A, delayed recall)	311	9.53	4.1
	Rey Auditory Verbal Learning Test total learning (sum of trials 15)	316	41.69	9.27
	Rey Auditory Verbal Learning Test short-term delayed recall (trial 6)	315	8.25	3.26
	Rey Auditory Verbal Learning Test long-term delayed recall (trial 7)	315	7.83	3.49
	Benton Visual Retention Test	316	11.99	1.76
Language	Boston Naming Test – 30 items	316	25.21	3.48
	Semantic Fluency (animals)	316	16.18	4.47
Visuospatial function	Block Design	316	22.39	7.83
Executive function	Controlled Oral Word Association Test (FAS)	316	37.9	12.09
	Trail Making Test B	316	114.4	51.75

Sulcal features

The procedures of measuring cortical sulcal span and global sulcal index have been described in Chapter 3.2. In brief, the T1 – weighted MRI scans were processed by sulcal extraction and identification pipeline which combined by SPM and Brainvisa software. After the cortical sulci were extracted and identified, we computed the regional cortical sulcal span and global sulcal index in individual.

In this study, five primary and secondary fissures, including superior frontal sulcus in frontal lobe, intra-parietal sulcus in parietal lobe, superior temporal sulcus in temporal lobe, and interlobar sulci of central sulcus and Sylvian fissure, were selected for investigation from each hemisphere (Figure 5.1) . These sulci were chosen because: (1) they are present in all individuals; (2) they are large and relatively easy to identify for facilitating error detection; (3) they are located on different cerebral lobes; and (4) all five sulcus are located on the lateral convex hemispheric surface, thus avoiding the potential artifact induced by the necessity to manually identify the AC-PC line. We carefully carried out visual inspection of the extraction and labeling for each individual scan in its 3D image and the mislabeled sulci were manually corrected. Approximately 10% (central sulcus) to 40% (superior frontal sulcus) sulci required manual correction in our study. The similar selection method has recently been applied to the study of cortical morphology in cerebral small vessel diseases (Jouvent et al., 2008) and a normal aging study (Kochunov et al., 2008).
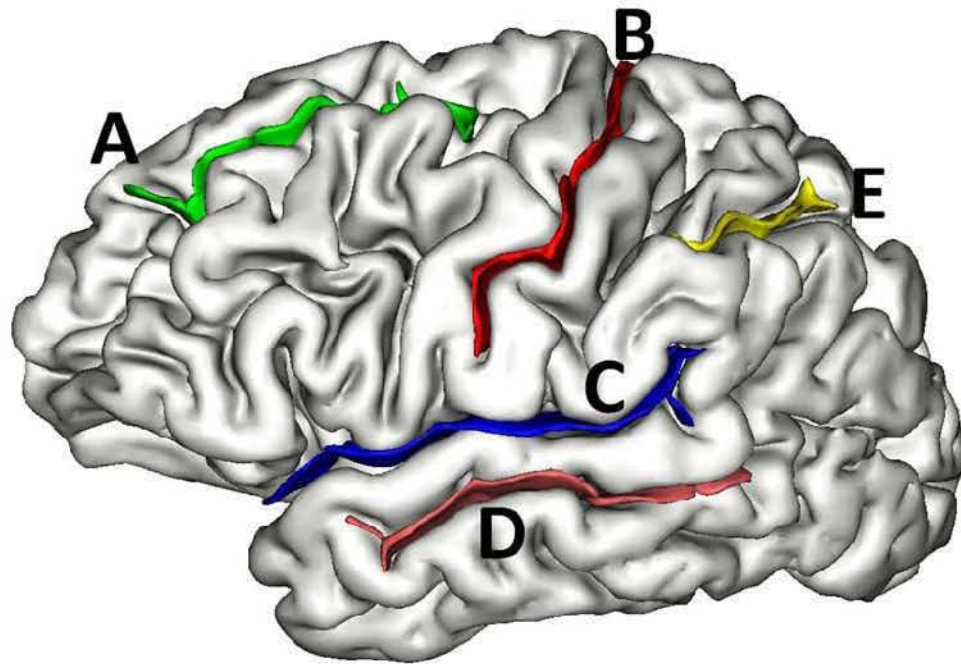
Figure 5.1. Measurements were performed for the following sulcal structures: superior frontal sulcus (A) in frontal lobe, interlobar sulci of central sulcus (B) and Sylvian fissure (C), superior temporal sulcus (D) in temporal lobe and intra-parietal sulcus (E) in parietal lobe.

Morphological analysis of cortical thickness

The procedures of measuring cortical thickness have been described in Chapter 3.3. In the present study, the average thicknesses for 34 regional areas were calculated for each area of cortex parcellated.

Statistical analysis

Raw neuropsychological assessment scores were transformed to z scores based on sample means and standard deviations, and domain composite scores were calculated by averaging z scores of the component tests. The signs of the Z scores of TMTA and TMTB were reversed, so that for all composites of cognitive domains, more positive scores represented better performances. Significant inverse relationships were observed between age and performances on all neuropsychological measures therefore we controlled the age effect in this study. In all the analyses, total intracranial cavity volume (ICV) was also used as a covariate to control for individual brain size because the brain size had a significant positive correlation with g-SI ($r = 0.20$, $p < 0.001$) and average sulcal span ($r = 0.13$, $p < 0.001$).

The effects of sulcal features including g-SI and sulcal span (SS) factors were tested on the five cognitive domain scores using multivariate analysis of covariance (MANCOVA), controlling for demographic effects, i.e. age, sex and years of education. Sex was treated as a fixed factor of 2 levels (male and female), hemisphere as a within-

subjects factor of 2 levels (left and right), region mark as a within-subjects factor of 5

levels (five different sulcus) and age and years of education as continuous covariates in

separate general linear models investigating the relationship between sulcal

morphology and cognitive function. An interaction effect between hemisphere, sex and

region was subsequently tested. If the interaction effect was found to be significant, we

then separated the model by the simple effects in the subsequent correlation analyses.

Partial correlation and linear regression were then used to investigate the relationship

between cognitive domains and sulcal feature after controlling for the other factors. We

also examined the relationship between cortical thickness and cognitive scores using

partial correlation after correcting for age, sex, years of education and brain size. The

false discovery rate (FDR) was used for the multiple comparison corrections.

5.3. Results

Cortical sulci

We found that g-SI significantly decreased with advancing age ($F_{(1, 622)}$ = 5.822, p =

0.016) and the widths of all five sulcal spans increased significantly with age (Wilks's

Lambda = 0.830, $F_{(6, 620)}$ = 21.134, $p < 0.001$,), after controlling for sex, ICV,

scanner and hemisphere. Therefore, to investigate the correlations between cognitive

function and sulcal features, we treated age as a covariate on the change of sulcal

morphology.

Globally, partial correlation analysis showed there were positive correlations between g-SI and the performances in most cognitive domains, namely processing speed (r = 0.104, p = 0.009), memory(r = 0.109, p = 0.006), language(r = 0.118, p = 0.003) and executive function (r = 0.126, p = 0.002), but not visuospatial function (r = 0.062, p = 0.122), after controlling for age, sex, education and ICV. The finding indicated higher complexity of sulcal folds reflected better cognitive function.

Regionally, the results of age-uncorrected and age-corrected correlation analyses between the five cognitive domains and the five sulcal spans for the two hemispheres are presented in Table 5.3. Briefly, a large number of correlations between sulcal spans and performances in cognitive domains were negative, meaning that wider sulcal spans reflected poorer cognitive performances. Of the five cognitive domains, processing speed performances most strongly correlated with sulcal spans. Processing speed score was negatively correlated with sulcal span in bilateral sylvian fissures (left: r = -0.154, p = 0.007; right: r = -0.123, p = 0.031), bilateral intraparietal sulci (left: r = -0.148, p = 0.009; right: r = -0.136, p = 0.016), bilateral superior frontal sulci (left: r = -0.139, p = 0.014; right: r = -0.156, p = 0.006) and bilateral superior temporal sulci (left: r = -0.173, p = 0.002; right: r = -0.192, p = 0.001), after age correction. With respect to memory, before controlling for age effects, memory scores were negatively correlated with spans of all sulci except the central sulcus, but these correlations were not significant after age correction. Although visuospatial ability did not significantly correlate with g-SI, it had a negative correlations with sulcal span, especially with the right superior frontal sulcus

(r = -0.168, p = 0.003) and bilateral superior temporal sulci (left: r = -0.138, p = 0.015; right: r = -0.123, p = 0.031), after controlling for age. Negative correlations between language performance and sulcal span were detected widely in both hemispheres; however, after controlling for age, most correlations with right hemispheric sulci became non-significant. Age-corrected correlations with language were significant with the left intraparietal sulcus (r = -.128, p = 0.023), left superior temporal sulcus (r = -0.164, p = 0.004) and bilateral superior frontal sulci (left: r = -0.112, p = 0.049; right: r = -0.116, p = 0.041). The performance in executive function was negatively correlated with sulcal span in all sulci except central, but after correcting for age effects, only left superior temporal remained a significant correlation (r = -0.154, p = 0.006). We used FDR to calculate the FDR thresholds for p values, and 0.031, 0.004 and 0.003 were used for the multiple comparisons for processing speed and language and spatial, respectively in the partial correlation analysis between SS and cognitive domains after controlling for age, sex, education and brain size.

Table 5.3. Age-uncorrected (UNCORR.) and age-corrected (AGE-COR.) partial correlation between regional right (R)/left (L) sulcal span and cognitive function scores for the elderly subjects (n = 316), after controlling for sex, education and brain size.

Sulcal span		Processing Speed		Memory		Language		Spatial		Executive	
		UNCORR.	AGE-COR.	UNCORR.	AGE-COR.	UNCORR.	AGE-COR.	UNCORR.	AGE-COR.	UNCORR.	AGE-COR.
Sylvian fissure	L	-0.226**	-0.154**	-0.132**	-0.053	-0.145**	-0.087	-0.167**	-0.097	-0.159**	-0.104
	R	-0.191**	-0.123**	-0.128**	-0.055	-0.102	-0.046	-0.154**	-0.089	-0.099	-0.046
Intraparietal	L	-0.233**	-0.148**	-0.158**	-0.067	-0.193**	-0.128*	-0.167**	-0.085	-0.127**	-0.061
	R	-0.234**	-0.136**	-0.161**	-0.057	-0.178**	-0.103	-0.212**	-0.122*	-0.044	0.041
Central	L	-0.049	0.046	-0.055	0.036	-0.091	-0.025	-0.07	0.012	0.011	0.081
	R	-0.087	-0.007	-0.033	0.051	-0.099	-0.041	-0.147**	-0.08	0.03	0.094
superior frontal	L	-0.233**	-0.139**	-0.146**	-0.044	-0.184**	-0.112*	-0.168**	-0.077	-0.063	0.016
	R	-0.240**	-0.156**	-0.114*	-0.019	-0.181**	-0.116*	-0.242**	-0.168**	-0.165**	-0.102
superior temporal	L	-0.235**	-0.173**	-0.147**	-0.079	-0.212**	-0.164**	-0.197**	-0.138*	-0.200**	-0.154*
	R	-0.249**	-0.192**	-0.130**	-0.066	-0.128*	-0.08	-0.178**	-0.123*	-0.143**	-0.098

*statistically significant at p < 0.05
**statistically significant at p < FDR threshold

The sulcal feature related interaction effects of g-SI/SS×sex and g-SI/SS×hemisphere on cognitive domains were investigated in 14 separate models using MANCOVA, and the main fixed factors of sex, age, ICV, year of education, and hemisphere were controlled for. Our results showed no significant cognitive function related interaction effects of g-SI×sex (Wilks's Lambda = 0.993, F (5,619) = 0.860, p = 0.508), g-SI×hemisphere (Wilks's Lambda = 1.00, F (5,619) = 0.025, p = 1.000), SS×sex or SS×hemisphere, suggesting no sex-differences or hemispheric asymmetry on g-SI or SS in relation to cognitive function. We therefore combined the data of male and female subjects, controlling for sex as a fixed factor in the analysis. When the sulcal feature related interaction effects of SS×region on performances in cognitive domains were tested, we found significant regional interaction effects of region×SS on performances in the domains of processing speed (F (5, 3774) = 2.943, p = 0.012) and executive function (F (5, 3774) = 3.067, p = 0.009), which suggested that the cognitive functions were associated with sulcal span changes differently in different regions (Table 5.3). Furthermore, using MANCOVA, we found that central sulcus had no significant relationship with performances in any of the five cognitive functions (left: Wilks's Lambda = 0.985, F (5,304) = 0.901, p = 0.480; right: Wilks's Lambda = 0.969, F (5,304) = 1.925, p = 0.090), while the left superior temporal sulcus showed the highest sensitivity, being negatively associated with performances in all five cognitive domains (Wilks's Lambda = 0.957, F (5,304) = 3.459, p = 0.009), after controlling for the effects of age, sex and brain size. Linear regression analysis showed that the left superior

68

temporal sulcus had a significant negative relationship with performances in four cognitive domains, i.e. processing speed (β = -0.284, t = -3.023, p = 0.003), language (β = -0.286, t = -2.916 p = 0.004), visuospatial (β = -0.213, t = -2.406, p = 0.017) and executive function (β = -0.258, t = -2.738, p = -0.007) (Figure 5.2), after controlling for age, sex and education.
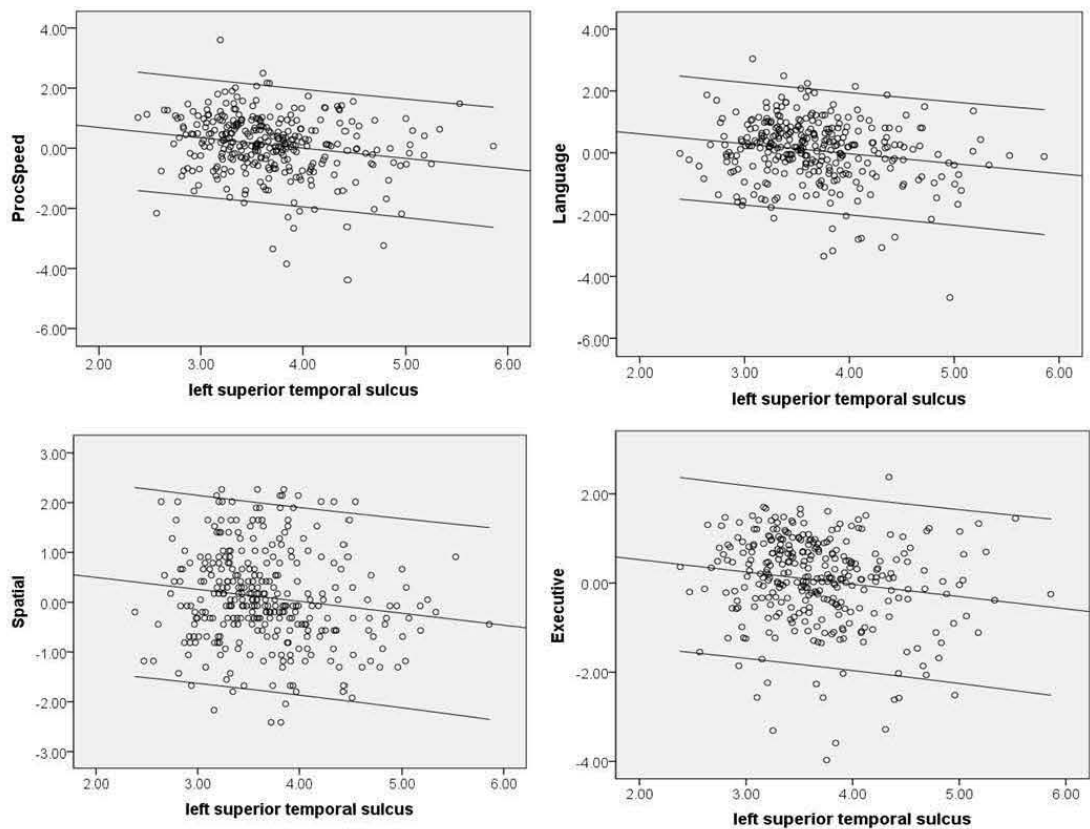
Figure 5.2. Scatter plots and regression lines for left superior temporal sulcus (mm) vs. z-scores of processing speed, language, visuospatial and executive functions.

The z-scores have been correcting for age, sex and years of education.

Cortical thickness

Similar to the correlations between sulcal span and cognitive performances, after controlling for age, sex, education and ICV in partial correlation analysis, we have also found some significant correlations between cortical thickness and cognitive scores. The cortical thickness of temporal region and front region showed significant correlations with many cognitive performances, including, left superior temporal gyrus and visuospatial ($r = 0.132$, $p = 0.030$); left middle temporal gyrus and visuospatial ($r = 0.130$, $p = 0.033$), left superior frontal gyrus with memory ($r = 0.142$, $p = 0.019$), left middle frontal gyrus with memory ($r = 0.191$, $p = 0.002$), left superior temporal gyrus with memory ($r = 0.159$, $p = 0.009$) and left middle temporal gyrus with memory ($r = 0.136$, $p = 0.025$). Correlations between language performance and cortical thickness were also detected in left superior parietal cortex ($r = 0.146$, $p = 0.016$), left interior parietal cortex ($r = 0.182$, $p = 0.003$) and left middle temporal gyrus($r = 0.144$, $p = 0.018$). However, none of the above correlations survived FDR corrections.

5.4. Discussion

The aim of the current study was to examine the relationship between cognitive function and the fold geometry of a set of sulcal regions in an elderly population. It has previously been shown that advancing age leads to an increase in the widths of sulci and a decrease in g-SI (Kochunov et al., 2005; Liu et al., 2010), as well as a decline in neuropsychological performances (O'Sullivan et al., 2001). Age-related cognitive changes in the elderly are possibly related to age-related brain structure changes (Raz

and Rodrigue, 2006). Therefore our findings of the correlations between cognitive functions and cortical sulcal variability were consistent with our predictions.

We found that some correlations between cognitive domains and sulcus spans were not significant after controlling for age, especially for memory and executive domains. The sulcus-related correlations of some cognitive domains, such as processing speed, were significant after age correction. The impact of controlling for age reflects the fact that age-related structural change can partially mediate the correlations between cognition and brain structure (Raz and Rodrigue, 2006). A recent study reported that the significant correlations between cognitive domains and cortical thickness became weaker or became non-significant in most regions after correcting for age (Chee et al., 2009). Conversely, the detection of significant sulcus-related correlations of certain cognitive domains such as processing speed after age correction indicated that regionally specific changes in sulcal morphology are associated with specific cognitive function.

Cognitive functions and g-SI

The mechanism involved in the plasticity of the nervous system is thought to support cognition (Burke and Barnes, 2006). It has also been suggested that an increase in the number of neurons results in surface expansion (Penttilä et al., 2009). As the definition suggest, g-SI describes the structural properties of the folding surface. Therefore, the mechanism might explain our observations of the association between g-SI measure

and cognitive performance. The cortical folding process that ultimately produces the mature sulco-gyral pattern is mediated by forces that stem from GM thickness and WM connectivity, which present associations with cognition. Moreover, g-SI also reflects the cortex gyrification. Mangin and colleagues (2010) suggested deviations of cortex gyrification were related to clinical symptoms and cognitive deficits. In our study, lower g-SI was associated with worse cognitive performance. A recent study documented that the gyrification index of mild Alzheimer's disease patients is significantly lower than control subjects (King et al., 2010). Our subjects were elderly individuals who did not have a diagnosis of dementia. However, a significant proportion had memory complaints or mild decrements in cognitive performance, and the presence of subclinical neurodegenerative or vascular pathology was quite likely. It is possible that such pathology contributed to both sulcal width as well as cognitive deficits and may underpin some of this relationship. Our choice of an older population for such a study was due to the fact that older individuals show greater variability in sulcal width and the relationship with cognitive function is more likely to be apparent. While we have not examined a younger population on this measure, we suspect that the same relationship is not likely to be present in younger individuals. In summary, we suggest that in elderly individuals, the more complex the sulcal folds globally in the brain, better the cognitive function of the individual.

Cognitive functions and sulcal span (SS)

Processing Speed (PS)

As a basic measure of processing efficiency, processing speed is likely to be influenced by the integrity of sensory and pattern recognition processes which are dependent upon the integrity of the brain (Peers et al., 2005; Salthouse, 1996; Tisserand et al., 2000), including both grey and white matter (Dow et al., 2004; Turken et al., 2008; Wen and Sachdev, 2004). In addition, decline in processing speed is prominent in the elderly, and becomes even more prominent during the time course of neurodegenerative dementias (Hedden and Gabrieli, 2004, 2005; Wen et al., 2011). Therefore, a good correspondence between PS and sulcal span (SS) was expected in the elderly. In our study, after controlling for age, years of education and brain volume effects, PS appeared to have the most prominent correlation with SS among all the cognitive domains. The sulcal deformation related with processing speed was detected in the bilateral Sylvian fissures, bilateral intraparietal sulci, bilateral superior temporal sulci and bilateral superior frontal sulci, but not with the central sulci. The correlation with the Sylvian fissure may reflect the functions of temporoparietal junction cortex which is at the posterior end of the Sylvian fissure. Further, the temporoparietal junction lesions may lead to the decrease of speed of stimulus identification which is reflected in the speed of processing (Peers et al., 2005). The deformation of superior temporal sulcus (STS) may reflect morphologic change of superior temporal gyrus, which includes primary auditory cortex and Wernicke's area, an important region for the processing of speech (Cuenod et al., 1995). PS did not correlate with the central sulcus, which

separates the frontal from the parietal lobe; while PS had negative correlations with superior frontal sulcus and intraparietal sulcus. Decreased activation of the frontal lobe has been observed in slower and less accurate groups relative to controls in tasks designed to assess reaction time and speed of processing (Rypma et al., 2007). In addition, decreased activation of the frontal and parietal lobes was detected in groups with processing speed deficits in a recent fMRI study (Genova et al., 2009). The correlation with the frontal sulcus was also consistent with prior studies which found a significant correlation between sulcal span in frontal lobe and PS (Kochunov et al., 2010). Processing speed had also been considered as an effective tool for clinical detection of neurological disorders (Keefe et al., 2006). Therefore, the extensive and strong correlations between cortical surface and processing speed may indicate the value of sulcal geometry in clinical diagnosis.

Memory

When age-related variance was taken into account, the sulcal spans did not relate to memory performance. There are a number of possible explanations for this: i) Memory function is largely dependent upon the integrity of subcortical structures such as the hippocampus (Golomb et al., 1994), parahippocampal gyrus (Jack et al., 1992), maxillary bodies, etc, the size of which is not reflected in the sulcal geometry measured in this study. ii) The memory functions might be affected mainly by substantial structure losses, leading to a threshold effect (De Leon et al., 1997), iii) While the dorsolateral prefrontal cortex and the anterolateral temporo-polar regions are important

for retrieval of memory (Markowitsch, 1995), there may be significant redundancy in the system for this not to manifest in a relationship between memory function and the widths of frontal sulci or the Sylvian fissures, over and above what is accounted for by age.

Language

A review by Vigneau and colleagues (2006) indicated that the left inferior parietal regions, left inferior frontal gyrus, left middle frontal gyrus, left superior temporal gyrus and the left supramarginal gyrus were organized into two neural components dedicated to speech, sound perception, and production: a fronto-temporal auditory-motor network and a fronto-parietal loop for phonological working memory. In addition, superior temporal gyrus and inferior frontal gyrus played an important role in semantic, phonological processing and sentence comprehension. Our observations of associations between language performance and sulcal span in left intraparietal sulcus (above the horizontal portion of the inferior parietal regions), left superior frontal sulcus (above the horizontal portion of inferior frontal gyrus and middle frontal gyrus) and left superior temporal sulcus (below the horizontal portion of superior temporal gyrus) are consistent with the above model.

Visuospatial function

Visuospatial functions have been consistently associated with predominantly right hemispheric regions (Marshall and Fink, 2001). The parietal cortex has been shown to code for the location of visual stimuli (Sereno and Huang, 2006), and lateral intraparietal cortex has been found to be involved in the control of spatial attention (Beauchamp et al., 2001; Hagler et al., 2007). Hagler and Sereno (2006) found that the superior frontal cortex played an important role in the attention to objects in a particular spatial location. Therefore, good performance on visuospatial function seems to be indicative of appropriate functioning of the lateral intraparietal area and frontal cortex, especially in right hemisphere. These expectations are consistent with our finding that there is a significant correlation between visuospatial ability and right superior frontal sulcus, and the right intraparietal sulcus.

Executive function

Executive function has generally been referred to as a "higher-level" cognitive function and is thought to be attributed to the anterior brain regions such as the frontal lobes (Reitan and Wolfson, 1994). We found significant correlations between superior frontal sulcus and executive task, but the correlation became non-significant after correcting for age effects. This lack of an independent relationship may be due to redundancy in the brain systems underlying executive function, such that width of one frontal sulcus may not relate to function is this domain. A recent review study also found inconsistent support for the historical association between executive functions and the frontal lobes

and they discussed the lack of direct association between damage to the prefrontal cortex and poor performance on executive task (Alvarez and Emory, 2006). After correcting for age, we found that only the superior temporal sulcus remained significantly associated with executive tasks. This may, we suggest, be related to the verbal aspects of the executive tasks.

Superior temporal sulcus (STS) and cognitive functions

Our most robust findings associated with cognitive function were in relation to the superior temporal sulcus. The STS is the main sulcal landmark of the external temporal cortex, and the deformation of STS might reflect a morphologic change of the superior temporal gyrus, which includes the primary auditory cortex and Wernicke's area, and is an important region for the processing of speech (Cuenod et al., 1995). STS as a landmark is also inside the paralimbic belt and was found to be similarly affected by the age-related pathologic process (Mega et al., 1998). Furthermore, the STS extends along the entire lateral ventricle and crosses the superior temporal sulcus multisensory area, which is important for integrating auditory and visual information (Zheng et al., 2010). In summary, because of the breadth of the area that involves the STS, the widespread correlates of cognitive function with STS were not unexpected. Our data suggest that sulcal width of the STS might be a useful biomarker of cognitive dysfunction if one sulcal size is to be selected for measurement.

Comparison with cortical thickness analysis

In our study, both cortical thickness and sulcal span were found to correlate with cognitive performances in the domains of language, visuospatial and executive functions in similar regions before FDR correction. However, after using FDR for multiple comparison correction, no significant correlations between cortical thickness and cognitive functions were found. This finding was consistent with the results of the study by Chee and others (Chee et al., 2009). On the other hand, we observed significant associations between processing speed and both g-SI and local SS in the cortical surface analysis even after FDR correction. The cortical surface area and cortical thickness are essentially unrelated genetically and they are two distinct sources of genetic influences (Panizzon et al., 2009).Therefore, there is the possibility that the sensitivity of the correlations between cognitive functions and cortical thickness is different from that between cognitive function and sulcal span. The link between processing speed and sulcal span is also consistent with the findings in Kochunov et al (2010).

Limitations of the study

Firstly, this is a cross-sectional examination and does not permit a causal inference between structural change and cognitive function. Because age-related cognitive deficits are best determined in a longitudinal study, in the next work, we will use our wave 2 scans which were taken two years after wave 1 scans to carry out a longitudinal study. Second, as our sample was aged 70-90 years, our findings are restricted to the

elderly. Third, since our sample only included those who were willing to undergo a MRI scan, the participants were probably physically healthier and slightly higher functioning than those who did not agree to undergo a scan. Nevertheless, we consider it unlikely that this would have influenced the salient findings of our study.

5.5. Summary

We report widespread correlations of cortical surface anatomy, especially in frontal and temporal regions, with cognition in non-demented elderly individuals. To our knowledge, this is the first study to examine 3D cortical sulcal patterns in healthy elderly with multiple cognitive domains. The salient findings are that processing speed has a broad and dispersed range of correlations with the cortical surface, with the strongest correlation being with the superior temporal sulcus, while no significant relationship between sulcal morphology and memory was detected. Globally, the complexity of sulcal folds is associated with better cognitive function in older individuals, after age-related changes have been accounted for. Cortical surface anatomy may serve as potential biomarker of cognitive function in the elderly and is worthy of further study.

CHAPTER 6: CORTICAL SULCI AND ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is characterized by an insidious onset of progressive cerebral atrophy and cognitive decline. Previous research suggests that both global and regional measures of sulcal morphology are associated with cognitive function in elderly individuals, and the aim of the present study was to investigate sulcal morphology in patients with AD. Moreover, we also computed average cortical thickness in eight areas side of sulci and observed their changes in AD. The sample contained 161 subjects, comprising 80 normal controls, 57 patients with very mild AD, and 24 patients with mild AD. From 3D T1-weighted brain scans, automated methods were used to calculate an index of global sulcal fold complexity and the width of five individual sulci: superior frontal, intra-parietal, superior temporal, central, and Sylvian fissure. The main findings are that global sulcal fold complexity decreased with increasing severity of AD, and that the width of all individual sulci investigated other than the intra-parietal sulcus was greater in patients with mild AD than in controls. It was also found that cognitive functioning, as assessed by Mini-Mental State Examination (MMSE) scores, decreased as global sulcal fold complexity decreased. MMSE scores decreased in association with a widening of all individual sulci investigated other than the intra-parietal sulcus. The results suggest that abnormalities of cortical sulci are characteristic of patients with even very mild AD, and could thus facilitate the early diagnosis of this condition.

6.1. Introduction

As the most common cause of dementia, Alzheimer disease (AD) is characterized by an insidious onset of cerebral atrophy and progressive cognitive decline (Braak and Braak, 1996; Rogan and Lippa, 2002). Brain regions showing abnormalities in AD, including the paralimbic and heteromodal association areas, were initially identified using postmortem brain tissue (Arnold et al., 1991; Braak and Braak, 1996; Morrison and Hof, 2002). More recently, magnetic resonance imaging (MRI) has been used to quantitatively study the neuroanatomic abnormalities of individuals with AD in vivo. MRI-based investigations have utilized volumetric measures of either regions of interest (ROIs) (He et al., 2007; Jack et al., 2004; Shi et al., 2009; Whitwell et al., 2007) or the whole brain (Fotenos et al., 2005; Sluimer et al., 2008), VBM (Chetelat et al., 2005; Hamalainen et al., 2007; Karas et al., 2003; Li et al., 2008; Wen et al., 2006), and cortical thickness (Dickerson et al., 2009; Im et al., 2008c). Across these studies, AD has often been associated with atrophy or cortical thinning in a number of brain regions, including frontal (Hamalainen et al., 2007; Im et al., 2008c; Whitwell et al., 2007), temporal (Chetelat et al., 2005; Hamalainen et al., 2007; Im et al., 2008c; Whitwell et al., 2007), parietal (Im et al., 2008c; Whitwell et al., 2007) and hippocampal (Chetelat et al., 2005; Frisoni et al., 2010; Hamalainen et al., 2007; Jack et al., 2004; Shi et al., 2009; Whitwell et al., 2007).

Variations of cortical folding morphology offer another approach to investigating

neuroanatomic differences that have received recent interest following the development

of sophisticated 3D-based image-processing techniques (Mangin et al., 2010). Sulcal

folds are the principal surface landmarks of the human cerebral cortex and exhibit

structurally complex patterns (Welker, 1988) that are postulated to reflect underlying

connectivity (Van Essen, 1997). Indeed, cortical folding patterns have been used to

predict cytoarchitecture (Fischl et al., 2008). In addition to being a macroscopic probe

for hidden architectural organization, folding geometry may also provide information

on developmental events (Mangin et al., 2010). Recent studies have identified

morphological differences in the sulci of some professional groups, including musicians

(Li et al., 2009), and in patients with psychiatric and neurological conditions like

schizophrenia (Cachia et al., 2008) and bipolar disorder (Penttilä et al., 2009). The

sulcal folding patterns associated with mild cognitive impairment (MCI) and AD have

also been investigated, with Im et al. (2008b) finding that the sulci of individuals with

either of these conditions had less curvature (reflecting greater widening) and depth

than those of cognitively normal controls. These differences were observed to be the

largest in the temporal lobe.

The present study aims to expand upon previous research into sulcal morphology in AD

in several important ways. First, we obtained global measurements of sulcal

morphometry using the global sulcal index (g-SI). This is a new index of sulcal fold

complexity whereby a larger g-SI reflects a greater degree of folding. Our group

previously found that g-SI not only decreases with age (Liu et al., 2010), but also with cognitive decline in the elderly (Liu et al., 2011). We thus hypothesized in the present study that individuals with AD would have a lower g-SI than cognitively normal controls. Second, the earlier study by Im et al. (2008b) investigated sulcal morphology at the lobal level. Our investigation was more fine-grained than this, with analyses conducted at the level of five individual sulci. We previously found the spans of these sulci to be correlated with age (Liu et al., 2010) and cognitive function (Liu et al., 2011) in the elderly. Third, we explored relationships between Mini-Mental State Examination (MMSE) scores and sulcal measures. The MMSE is widely used in both clinical and research settings to assess patients with AD (Holsinger et al., 2007), but associations between its scores and either g-SI or individual sulcal spans do not appear to have been investigated. Fourth, previous studies have reported on patients with a severity of AD ranging from mild to moderate. In the present study, we focused specifically on even early stages of AD, including the very mild. Understanding the brain changes associated with AD at its mildest stage may facilitate the development of early interventions for this debilitating condition.

6.2. Methods

Subjects

The subjects were obtained from the Open Access Series of Imaging Studies (OASIS) database (http://www.oasis-brains.org) (Marcus et al., 2007). Data from the database have been published in previous cortical thickness study (Dickerson et al., 2009).The

minimum age of early-stage AD patients in the database is 62 years; hence we restricted the analysis to those participants in the normal group with observations starting at age 62 years and older. One hundred and ninety-three right–handed subjects aged at or above 62 years were selected from the database of OASIS. Data from thirty-two subjects were excluded from the analysis because of failure in various imaging processing steps, including skull stripping (five subjects), segmentation (six subjects) and sulcal recognition (twenty-one subjects). The included subjects were classified into healthy elders (n = 80) and early-stage AD patients (n = 81) by using the Clinical Dementia Rating scale (CDR) (Morris, 1993; Morris et al., 2001). Fifty-seven of the eighty-one AD patents who had a CDR score of 0.5 were assigned to the very mild category which ranged in age from 62 to 92 (mean age = 75.79; SD = 7.31), and the remaining twenty-four who had a CDR score of 1 were assigned to the mild category which ranged in age from 65 to 96 (mean age = 77.33; SD = 7.34). The eighty healthy controls (CDR = 0) ranged in age from 62 to 93 (mean age = 76.16; SD = 8.13). Cognitive function of all subjects was evaluated using the Mini Mental State Examination (MMSE) (Folstein et al., 1975). The control, very mild AD and AD groups had an average MMSE score of 28.88 (range, 25–30), 25.44 (range, 14-30) and 21.17 (range, 15-28), respectively. The demographic and clinical data of the participants are presented in Table 6.1. The group characteristics were compared using analysis of variance (ANOVA) with a Bonferroni *post hoc* test and a chi-square test. The age and sex did not differ significantly between the groups, but MMSE scores did.

Table 6.1 Demographic characteristics of controls and very mild AD and mild AD subjects

	Control (n = 80)	Very mild AD (n = 57)	Mild AD (n = 24)	$F/\chi^{2\ a}$	P
Age, years	76.2±8.1	75.8±7.3	77.3±7.3	0.34	0.716
Sex, M/F	22/58	25/32	6/18	4.83	0.089
MMSE score	28.9±1.3	25.4±3.7	21.2±3.5	80.48	<0.0001

a: F test, except for sex (χ^2 test)

Image acquisition

For each subject, three to four individual T1-weighted magnetization prepared rapid gradient-echo (MP-RAGE) images were acquired on a 1.5T Vision scanner (Siemens, Erlangen, Germany) within a single session. Head movement was minimized by cushioning and a thermoplastic face mask. The images were motion corrected and averaged to create a single image with high contrast-to-noise. The MP-RAGE parameters were empirically optimized for gray–white contrast (repetition time, 9.7 ms; echo time, 4.0 ms; inversion time, 20 ms; delay time, 200 ms; flip angle, 10°; orientation, sagittal; resolution, 256 × 256 matrix; slices, 128; thickness, 1.25 mm).

Sulcal features

The procedures of measuring cortical sulcal span and global sulcal index have been described in Chapter 3.2. In brief, for each hemisphere, we measured g-SI as the ratio between total sulcal area and outer cortical area and the average sulcal span for each of five sulci: superior frontal, intra-parietal, superior temporal, central, and Sylvian

fissure. All five sulci in this study are on the lateral convex hemispheric surface, thus negating the need to manually identify the AC-PC line and thereby avoiding the potential artifact induced by this.

Cortical thickness

The procedures of measuring cortical thickness have been described in Chapter 3.3. In the present study, we determined the average cortical thickness for each of eight sulci-related areas: inferior parietal lobule, superior parietal lobule, inferior temporal gyrus, superior temporal gyrus, middle temporal gyrus, postcentral gyrus, precentral gyrus and superior frontal gyrus

Statistical analysis

The group characteristics of sucal measures were compared using analysis of covariance (ANCOVA) and multivariate analyses of covariance (MANCOVAs) with Bonferroni post hoc test. g-SI was assessed using ANCOVA, with group (normal, very mild AD and mild AD) and hemisphere (left or right) entered as fixed factors. The repeated-measures multivariate analyses of covariance (MANCOVAs) were used to examine the group differences of the span in five regional sulci. The analyses treated the group (normal, very mild AD and mild AD) as between-subjects factors; sulcal region and brain hemisphere as repeated-measures factors. In present study, both age and sex did not differ between the groups (Table 6.1), therefore age and sex were not entered as covariates in group comparisons. Multivariate statistics (Roy's Largest Root

and related F statistic) were used to evaluate interaction effects involving repeated measures factors. If the group-related interaction effect was found to be significant, we then split the model by the main effects to investigate the interactive effect in subsequent analyses. *Post hoc* t tests were performed to investigate regional specificities and probe significant main or interactive effects, with Bonferroni corrections for post-hoc comparisons at a corrected p-value of 0.05. Additional analyses examined the association between MMSE and sulcal measures by using MANCOVA and partial correlation after correcting for age, sex and hemisphere. Group differences in the thickness measures were also investigated with MANCOVA for the eight areas. The false discovery rate (FDR) was used for multiple comparison corrections.

6.3. Results

Using ANCOVA, g-SI was found to be significantly differed between the groups ($F_{(2, 319)} = 30.19$, $p < 0.001$). There were significant stepwise reductions of g-SI starting from normal control to very mild AD to mild AD [control vs. very mild AD: 6.23% decrease in mean value ($p < 0.001$); very mild AD vs. mild AD: 9.84% decrease in mean value ($p < 0.001$); very mild AD vs. mild AD: 15.45% decrease in mean value ($p < 0.001$)], in pairwise comparisons with Bonferroni correction (Figure 6.1).
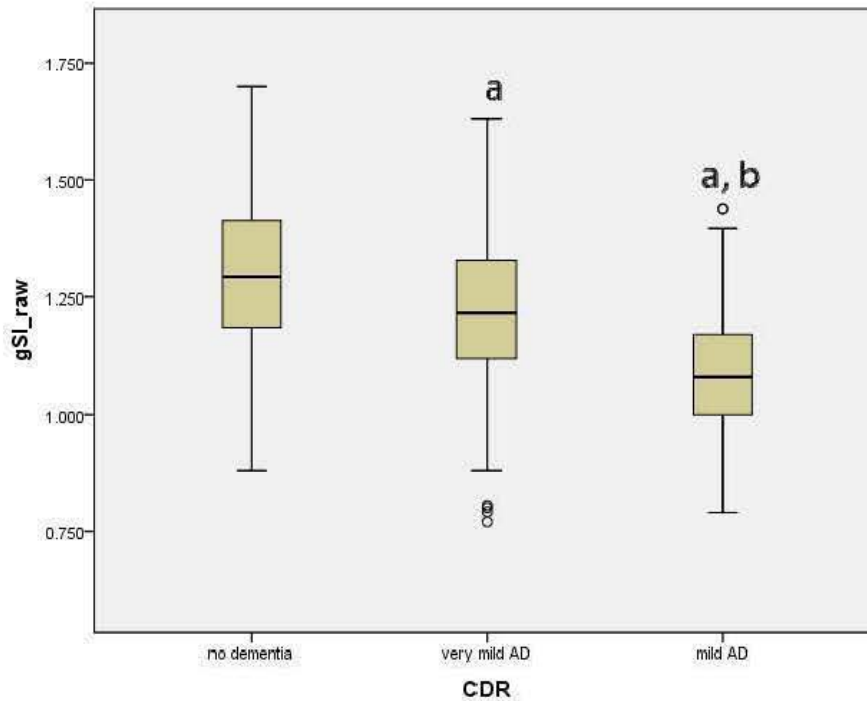
Figure 6.1. Box plots displaying the data distributions and differences in g-SI among the control, very mild AD and mild AD groups.

a: significantly differs from control (P < 0.001), b: Significantly differs from very mild AD (P < 0.001), with Bonferroni corrections for post-hoc comparisons

For the regional analysis of five cortical sulci, a significant main effect of the groups was revealed for sulcal spans ($F_{(2, 158)}$ = 6.468, p = 0.002), using repeated-measures MANCOVAs. The pairwise comparisons with Bonferroni corrections indicated that the sulcal span was significantly wider in mild AD than in controls (p = 0.001) or in very mild AD (p = 0.039). But the difference between control and very mild AD subjects in sulcal span was not significant (p = 0.595).

The MANCOVA also revealed a significant interaction effect between groups and sulcal region in sulcal span (Roy's Largest Root = 0.086, $F_{(4,156)}$ = 3.360, p = 0.011), which suggested that the sulci of specific regions were significantly different in different groups (normal, very mild AD and mild AD). In the post hoc t tests, compared with controls, mild AD subjects appeared significantly wider sulcal span in most sulci, which included superior frontal sulcus (p < 0.001), central sulcus (p = 0.004), Sylvian fissure(p < 0.001) and superior temporal sulcus (p < 0.001), except intraparietal sulcus (p = 0.126) (Table 6.2). Only in Sylvian fissure did very mild AD subjects show a significant wider sulcal span (P = 0.003) in comparisons to controls. It was detected that very mild AD subjects had significantly narrower sulcal span than mild AD subjects in the superior frontal sulcus (p = 0.001) and in superior temporal sulcus (p = 0.020). Figure 6.2 showed the box plots depicting the data distributions and differences in sulcal span among the control, very mild AD and mild AD groups. And Table 6.2 provides details of the measurements from these three groups of participants. Among the five sulci, the greatest AD-associated differences in sulcal span were detected in Sylvian fissure, showing an around 14% increase from normal control to mild AD in mean value (Normal: 5.56mm, mild AD: 6.37mm). No other additional significant interactive effects involving groups, region, or hemisphere were obtained.

Table 6.2 Statistical tests (MANCOVA) of group difference of the mean sulcal span (in millimetres) in five sulci

Sulcal structure	Normal(CDR = 0)	Very mild AD (CDR = 0.5)	Mild AD (CDR = 1)	F	P
Sylvian fissure	5.561	5.977	6.368	13.351	<0.001
intra-parietal sulcus	4.352	4.336	4.607	2.435	0.089
central sulcus	3.536	3.627	3.923	5.350	0.005
superior frontal sulcus	4.397	4.425	4.839	8.613	<0.001
superior temporal sulcus	3.992	4.120	4.449	7.938	<0.001
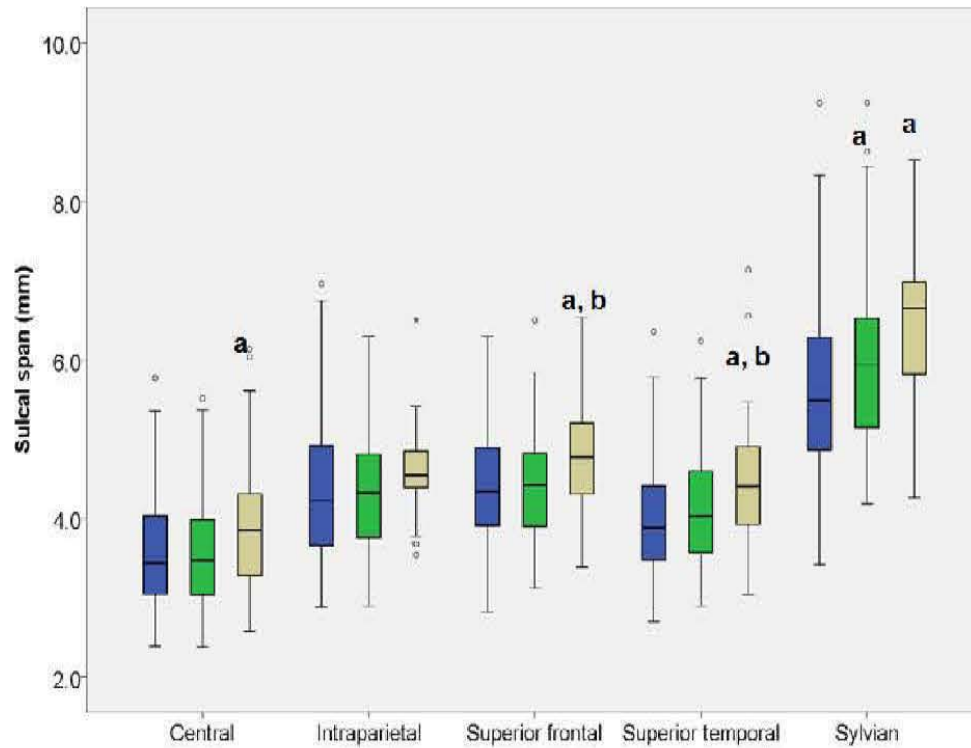
Figure 6.2. Box plots displaying the data distributions and differences in SS among the control (blue), very mild AD (green) and mild AD (brown) groups. **a:** significantly differs from control, **b:** Significantly differs from very mild AD, with Bonferroni corrections for post-hoc comparisons at a corrected p-value of 0.05.)

Relationships between sulcal measures and MMSE scores are shown in Table 6.3. There was a significant positive correlation between g-SI and MMSE score. Significant negative correlations between MMSE score and sulcal span were found for the Sylvian fissure, central, superior frontal and superior temporal sulci. The association between MMSE score and intra-parietal sulcus span did not reach the level of statistical significance after controlling for age.

Table 6.3 Age-unadjusted and Age-adjusted Correlations Between the sulcal span/ g-SI and the MMSE Scores, after controlling for sex

Sulcal structure g-SI/regional SS	Age- unadjusted Partial Correlation(r)	*Significance (P)[a]*	Age adjusted Partial Correlation (r)	*Significance (P)[b]*
g-SI	0.365	<0.001	0.392	<0.001
Sylvian fissure	-0.206	<0.001	-0.263	< 0.001
intra-parietal sulcus	-0.133	0.017	-0.151	0.058
central sulcus	-0.165	0.003	-0.180	0.024
superior frontal sulcus	-0.237	<0.001	-0.263	< 0.001
superior temporal sulcus	-0.245	<0.001	-0.306	< 0.001

a: The p value of 0.017 is set to equal an FDR of 0.05

b: The p value of 0.011 is set to equal an FDR of 0.05

Regarding to cortical thickness, an overall significant MANCOVA result indicated group differences in eight areas (Roy's Largest Root = 0.179, F $_{(8,140)}$ = 3.137, p = 0.003) which follow-up comparisons identified as mostly reflecting thinner cortical thickness in the mild AD group than in the normal group and in the very mild AD. Table 6.4 shows the mean cortical thickness of the normal, very mild AD and mild AD groups. Reductions in thickness in mild AD were found in all areas except postcentral gyrus. The thickness of the inferior temporal gyrus and superior temporal gyrus was thinner in the mild AD group than in the very mild AD group. Unlike the finding in intraparietal sulcus, the cortical thickness in parietal lobule showed significantly reduction in very mild AD and mild AD.

An additional ANCOVA test indicated the group difference in g-SI remained significant, even after controlling for the average cortical thickness of the whole brain ($F_{(2,154)}$ = 7.291, p = 0.001). The group difference in span of the superior temporal sulci and central sulci become nonsignificant after controlling for cortical thickness. However, the significant differences of sulcal span were still present in Sylvian fissure and superior frontal sulci after controlling for cortical thickness.

Table 6.4 Cortical thickness values of the normal, very mild AD, and mild AD groups

Cortical thickness, mm	Normal	Very mild AD	Mild AD	F^a	p^a
inferior parietal lobule	2.120	2.050^b	2.027^b	6.826	0.001
superior parietal lobule	1.975	1.898^b	1.877^b	7.026	0.001
inferior temporal gyrus	2.412	2.393	$2.303^{b,c}$	4.398	0.014
superior temporal gyrus	2.393	2.340	$2.246^{b,c}$	8.382	<0.001
middle temporal gyrus	2.421	2.391	2.318^b	4.249	0.016
post central gyrus	1.943	1.895	1.871	4.118	0.018
pre central gyrus	2.188	2.136	2.093^b	4.340	0.015
superior frontal gyrus	2.433	2.382	2.328^b	4.943	0.008

a Results of omnibus test across all three groups
b Significant difference from Normal with post-hoc Bonferonni test (p < 0.05)
c Significant difference from Very mild AD with post-hoc Bonferonni test (p < 0.05)

6.4. Discussion

The present study investigated changes in cortical surface morphology associated with early stage AD. Compared to cognitively normal controls, we found that individuals with early stage AD had less global sulcation, as measured by g-SI. The reduction in sulcation was greater for individuals with mild AD than for those with very mild AD. We also conducted a focused investigation of five particular sulci, and found the width of four of these to be greater in individuals with mild AD than in cognitively normal controls. AD is characterized by progressive cognitive decline (Braak and Braak, 1996; Rogan and Lippa, 2002), meaning the results of the present study are consistent with the previous finding that cognitive decline in the elderly is associated with decreases in sulcation and increases in sulcal span (Liu et al., 2011; Kochunov et al., 2010).

A previous study found sulcal widening in individuals with AD at the lobal level within each of the frontal, parietal, temporal and occipital lobes (Im et al., 2008b). The present study extends upon this work by finding AD-associated widening of particular intralobar sulci: the superior frontal and superior temporal. We found no difference in the width of the intra-parietal sulcus, while cortical thinning in parietal lobule was found. These findings suggest that the intra-parietal sulcus may not have been a major contributor to the parietal lobar effects observed by Im et al. or to the reduction in global sulcation we report here. Indeed, our findings of AD-associated widening specifically of the superior frontal and superior temporal sulci are consistent with the spatial distribution of neurodegenerative change in AD reported by post-mortem studies (Arnold et al., 1991; Braak and Braak, 1991). They are also consistent with VBM (Chetelat et al., 2005; Hamalainen et al., 2007; Karas et al., 2003; Li et al., 2008) and cortical thickness studies (Dickerson et al., 2009; Im et al., 2008a) in which GM atrophy was seen primarily in the frontal and temporal regions of individuals with mild AD.

GM atrophy of the frontal and temporal regions may underlie our finding that, of all five intra- and inter-lobar sulci investigated; the Sylvian fissure exhibited the largest increase in width between individuals with normal cognition and those with mild AD. It has previously been reported that reductions in gyral GM volume are associated with increases in sulcal width (Im et al., 2008b). As it separates the frontal and temporal

lobes, decreases in the volume of these structures should widen the Sylvian fissure. The observations of cortical thinning in temporal gyrus and frontal gyrus also match the expectations, which the Sylvian fissure lies between the temporal and frontal gyrus. Also noteworthy is that the Sylvian fissure was also the only sulcus for which we found width to differ between individuals with normal cognition and those with very mild AD. This suggests that, alongside g-SI, width of the Sylvian fissure could be a useful neuroanatomical marker of early-stage AD.

There may also be a role for g-SI in tracking the progression of AD, as we found that this relatively new index of sulcal morphology exhibited a progressive decrease from cognitively normal controls to participants with very mild AD, and from participants with very mild AD to participants with mild AD. This incremental decrease in sulcation with increasing severity of cognitive status is consistent with the progressive increase in sulcal widening from controls to MCI and from MCI to AD reported by Im et al. (2008b), and reflects the increase in clinical symptom severity from very mild AD to mild AD (Dickerson et al., 2009).

The significant increase of sulcal span in mild AD is still observed on Sylvian fissure and superior frontal sulcus, after controlling for cortical thickness. Previous studies have suggested that the width of cortical sulci is considered as markers reflecting integrity of both gray and white matter structure (Jouvent et al., 2011; Kochunov et al., 2008), while cortical thickness is treated as a typical feature to cortical gray matter

structure (Dickerson et al., 2008). Therefore, the significant changes of SS in AD may also be a result of white matter structural alterations. In line with this hypothesis, a pervious study has detected that a number of white matter regions were reduced in AD with parahippocampal, entorhinal, inferior parietal and rostral middle frontal white matter showing the strongest AD-associated reductions (Salat et al., 2009). In addition, the white matter hyperintensity, one of the major manifestations of vascular pathology, is frequently observed on T2-weighted FLAIR images in MCI and AD (Bigler et al., 2002). It is also suggested that the cortical surface area and cortical thickness are essentially unrelated genetically and they are two distinct sources of genetic influences (Panizzon et al., 2009).Therefore, although the changes of cortical thickness in AD may contribute to the changes of SS in AD, other effects, e.g. white matter abnormality may also lead to the alterations of SS. It is noteworthy that the differences in very mild AD and mild AD remain significant after controlling for cortical thickness. As the definition suggests, g-SI describes the structural properties of the cortical folding, not only reflecting brain cortical atrophy, but also cortex gyrification. Mangin and colleagues (Mangin et al., 2010) suggested that deviations of cortex gyrification were related to clinical symptoms and cognitive deficits. A recent study documented that the gyrification index of mild Alzheimer's disease patients is significantly lower than control subjects (King et al., 2010) which is consistent with our observation of lower g-SI in AD.

The differences in sulcal morphology between cognitively normal controls and participants with AD are complemented by our finding that MMSE scores were positively associated with g-SI and negatively associated with the span of each of four individual sulci (central, superior frontal, superior temporal, and Sylvian fissure). This supports our previous report of associations between cognitive test performance and sulcal morphology at both the regional and global levels in elderly individuals (Liu et al., 2011), and is not unexpected given the capacity of the MMSE to asses AD severity (Holsinger et al., 2007). Accordingly, there is consistency in our findings that the span of the intra-parietal sulcus neither differentiated between cognitively normal controls and participants with AD, nor had a statistically significant association with MMSE scores. On the other hand, cortical thinning in parietal lobe was observed in our study. However, our results of sulci do not exclude an involvement of the parietal lobe in the early stages of AD, which could involve metabolic changes more so than structural changes, or structural changes in parietal regions that minimally affect the intra-parietal sulcus (Jacobs et al., 2011).

The present study has a limitation in being cross-sectional, meaning that causal inferences between sulcal width and dementia severity cannot be made. An aim of future research should be to longitudinally track changes in g-SI and sulcal width within individuals who experience an increasing severity of AD, and to do so into the moderate and severe stages of AD that are beyond the very mild and mild levels that we report on here.

6.5. Summary

The study has demonstrated abnormalities of cortical sulci in very mild and mild AD, both globally, as measured by g-SI, and at the regional level of individual sulci. Whereas the global complexity of sulcal folds was seen to decrease with increasing severity of AD (from normal to very mild AD to mild AD), widening of individual sulci generally became apparent at the mild stage of AD. Supplementing these results are our findings of positive correlations between sulcal measurements and MMSE scores. Of the individual sulci investigated, the largest effects were found for the Sylvian fissure. There were no effects found for the intra-parietal sulcus. The results of the present study suggest that abnormalities of cortical sulci are an important and salient characteristic of patients in the early stages of AD, and could thus potentially aid in the timely and accurate clinical diagnosis of this debilitating neurodegenerative condition.

CHAPTER 7: SUMMARY AND FUTURE STUDY

7.1. Research summary

This thesis investigates morphological changes of cerebral cortex based on MRI in the early stage of AD to discover cortical features that may serve as potential markers of brain aging and the early stages of dementia. The project has developed into three subprojects to explore structural variability in an aging brain, cognitive aging and early stage AD. In the first sub-project, we measured the global sulcal indices (g-SIs) of both cerebral hemispheres and the average sulcal span in five prominent sulci from a large community cohort of 319 non-demented individuals aged 70–90 years. Our findings suggest that both age and sex contribute to significant cortical gyrification differences and variations in the elderly. To our knowledge, this is the first study to report global and regional cortical sulcal morphometry in a large sample of the elderly. The study establishes a reference for future studies of age-related brain changes and neurodegenerative diseases in the elderly. However, it is still not known how sulcal features relate to brain function. Therefore, in the second sub-project, we examined the relationship between cortical features and cognitive function in the same sample. The results showed the cognitive performances were correlated with sulcal features, but not with cortical thickness. The findings suggest that regionally specific sulcal morphology is associated with cognitive function in elderly individuals. In the previous two studies, we found the sulcal features to be correlated with age and cognitive function in the

elderly. In the third study, we hypothesized those individuals with AD, even if only mild, would present abnormalities of cortical sulci. The results are in line with the hypothesis. Therefore, to sum up, cortical sulci could be considered as potential markers of brain aging, cognitive function and the early stages of dementia, and could therefore potentially assist in the timely and accurate clinical diagnosis of this debilitating neurodegenerative condition.

7.2. Future directions

The present study has a limitation in being cross-sectional, so that causal inferences between structural changes and age/cognitive function/dementia severity cannot be made. An aim of our future research will be to longitudinally track changes in the cerebral cortex within individuals who experience an increasing severity of AD, and to do so into the moderate and severe stages of AD that are beyond the very mild and mild levels that we report here. Recently, the Alzheimer's Disease Neuroimaging Initiative (ADNI), a multi-site study across the United States and Canada, has shared their rich database with the public. Around 800 subjects over a 36-month period (200 normal controls, 400 MCI, and 200 AD) were enrolled in the project. Therefore, this ADNI population may be evaluated in further work for longitudinal tracking.

The present study only focused on the structural MRI. Multimodal neuroimaging measures, including sMRI, DTI and fMRI, have the potential to offer convenient biomarker windows into brain disorders (Jiang et al., 2008). A review paper has

suggested "Functional or structural MRI study alone has its own limitations and shortcomings. However, the combined analysis of these could provide a more nearly complete view of the problem" (Jiang et al., 2008). Therefore, further work may combine multimodal neuroimaging measures and employ advanced algorithms in multivariate analysis and classification such as non-negative matrix factorization (Guan et al., 2011) and linear discriminant analysis (Tao et al., 2007; Tao et al., 2009) to enhance the understanding of brain.

One of the goals of identifying biomarkers for AD is to develop useful tools or create new criteria for early diagnosis of AD based on the biomarkers obtained from neuroimaging technology. The newly proposed diagnostic criteria for AD must be validated in multiple large data sets (Frisoni et al., 2010) that were hard to access before. However, many institutes such as ADNI and OASIS have shared their rich data with the public to overcome the limitation of sample size. It would be interesting to develop early diagnosis protocols, which have good predictive power, for predicting of progression of normal to AD, using neuroimaging biomarkers and machine learning techniques.

REFERENCES

Alvarez, J.A., Emory, E., 2006. Executive function and the frontal lobes: a meta-analytic review. Neuropsychol Rev 16, 17-42.

Anderson, J.R., 1985. Cognitive psychology and its implications, 2nd ed. W.H. Freeman, New York.

Andersson, S., Barder, H.E., Hellvin, T., Lovdahl, H., Malt, U.F., 2008. Neuropsychological and electrophysiological indices of neurocognitive dysfunction in bipolar II disorder. Bipolar Disord 10, 888-899.

Antonova, E., Kumari, V., Morris, R., Halari, R., Anilkumar, A., Mehrotra, R., Sharma, T., 2005. The relationship of structural alterations to cognitive deficits in schizophrenia: a voxel-based morphometry study. Biol Psychiatry 58, 457-467.

Apostolova, L.G., Lu, P., Rogers, S., Dutton, R.A., Hayashi, K.M., Toga, A.W., Cummings, J.L., Thompson, P.M., 2008. 3D mapping of language networks in clinical and pre-clinical Alzheimer's disease. Brain Lang 104, 33-41.

Apostolova, L.G., Thompson, P.M., 2008. Mapping progressive brain structural changes in early Alzheimer's disease and mild cognitive impairment. Neuropsychologia 46, 1597-1612.

Apostolova, L.G., Thompson, P.M., Rogers, S.A., Dinov, I.D., Zoumalan, C., Steiner, C.A., Siu, E., Green, A.E., Small, G.W., Toga, A.W., Cummings, J.L., Phelps, M.E., Silverman, D.H., 2010. Surface feature-guided mapping of cerebral metabolic changes in cognitively normal and mildly impaired elderly. Mol Imaging Biol 12, 218-224.

Armstrong, E., Schleicher, A., Omran, H., Curtis, M., Zilles, K., 1995. The ontogeny of human gyrification. Cereb Cortex 5, 56-63.

Arnold, S.E., Hyman, B.T., Flory, J., Damasio, A.R., Van Hoesen, G.W., 1991. The topographical and neuroanatomical distribution of neurofibrillary tangles and neuritic

plaques in the cerebral cortex of patients with Alzheimer's disease. Cereb Cortex 1, 103-116.

Ashburner, J., 2009. Computational anatomy with the SPM software. Magn Reson Imaging 27, 1163-1174.

Ashburner, J., Friston, K.J., 2000. Voxel-based morphometry--the methods. Neuroimage 11, 805-821.

Australia, A., 2011. Dementia across Australia. Deloitte Australia.

Australian Bureau of Statistics, A.B.o.S., 2010. Population by Age and Sex, Australian States and Territories. Australian Bureau of Statistics, CANBERRA.

Bakkour, A., Morris, J.C., Dickerson, B.C., 2009. The cortical signature of prodromal AD: regional thinning predicts mild AD dementia. Neurology 72, 1048-1055.

Bang-Bon Koo, Kim, D.-S., 2010. Computer-Based Morphometry of Brain. International Journal of Imaging Systems and Technology 20, 9.

Barr, W.B., 1997. Examining the right temporal lobe's role in nonverbal memory. Brain Cogn 35, 26-41.

Bear, M.F., Connors, B.W., Paradiso, M.A., 2007. Neuroscience: exploring the brain, 3rd. edition ed. Lippincott Williams & Wilkins.

Beauchamp, M.S., Petit, L., Ellmore, T.M., Ingeholm, J., Haxby, J.V., 2001. A parametric fMRI study of overt and covert shifts of visuospatial attention. Neuroimage 14, 310-321.

Benton, A.L., 1967. Problems of test construction in the field of aphasia. Cortex 3, 32-58.

Benton, A.L., Spreen, O, 1996. Der Benton Test (7th ed.). Verlag Hand Huber, Bern.

Bigler, E.D., Kerr, B., Victoroff, J., Tate, D.F., Breitner, J.C., 2002. White matter lesions, quantitative magnetic resonance imaging, and dementia. Alzheimer Dis Assoc Disord 16, 161-170.

Blanton, R.E., Levitt, J.G., Thompson, P.M., Narr, K.L., Capetillo-Cunliffe, L., Nobel, A., Singerman, J.D., McCracken, J.T., Toga, A.W., 2001. Mapping cortical asymmetry and complexity patterns in normal children. Psychiatry Res 107, 29-43.

Bonnici, H.M., William, T., Moorhead, J., Stanfield, A.C., Harris, J.M., Owens, D.G., Johnstone, E.C., Lawrie, S.M., 2007. Pre-frontal lobe gyrification index in schizophrenia, mental retardation and comorbid groups: an automated study. Neuroimage 35, 648-654.

Braak, H., Braak, E., 1996. Evolution of the neuropathology of Alzheimer's disease. Acta Neurol Scand Suppl 165, 3-12.

Burke, S.N., Barnes, C.A., 2006. Neural plasticity in the ageing brain. Nat Rev Neurosci 7, 30-40.

Butman, J.A., Floeter, M.K., 2007. Decreased thickness of primary motor cortex in primary lateral sclerosis. AJNR Am J Neuroradiol 28, 87-91.

Cachia, A., Paillere-Martinot, M.L., Galinowski, A., Januel, D., de Beaurepaire, R., Bellivier, F., Artiges, E., Andoh, J., Bartres-Faz, D., Duchesnay, E., Riviere, D., Plaze, M., Mangin, J.F., Martinot, J.L., 2008. Cortical folding abnormalities in schizophrenia patients with resistant auditory hallucinations. Neuroimage 39, 927-935.

Chan, R.C., Shum, D., Toulopoulou, T., Chen, E.Y., 2008. Assessment of executive functions: review of instruments and identification of critical issues. Arch Clin Neuropsychol 23, 201-216.

Chee, M.W., Chen, K.H., Zheng, H., Chan, K.P., Isaac, V., Sim, S.K., Chuah, L.Y., Schuchinsky, M., Fischl, B., Ng, T.P., 2009. Cognitive function and brain structure correlations in healthy elderly East Asians. Neuroimage 46, 257-269.

Chen, K.H., Chuah, L.Y., Sim, S.K., Chee, M.W., 2010. Hippocampal region-specific contributions to memory performance in normal elderly. Brain Cogn 72, 400-407.

Chetelat, G., Landeau, B., Eustache, F., Mezenge, F., Viader, F., de la Sayette, V., Desgranges, B., Baron, J.C., 2005. Using voxel-based morphometry to map the structural changes associated with rapid conversion in MCI: a longitudinal MRI study. Neuroimage 27, 934-946.

Cho, S., Jones, D., Reddick, W.E., Ogg, R.J., Steen, R.G., 1997. Establishing norms for age-related changes in proton T1 of human brain tissue in vivo. Magn Reson Imaging 15, 1133-1143.

Coffey, C.E., Ratcliff, G., Saxton, J.A., Bryan, R.N., Fried, L.P., Lucke, J.F., 2001. Cognitive correlates of human brain ageing: a quantitative magnetic resonance imaging investigation. J Neuropsychiatry Clin Neurosci 13, 471-485.

Coffey, C.E., Wilkinson, W.E., Parashos, I.A., Soady, S.A., Sullivan, R.J., Patterson, L.J., Figiel, G.S., Webb, M.C., Spritzer, C.E., Djang, W.T., 1992. Quantitative cerebral anatomy of the ageing human brain: a cross-sectional study using magnetic resonance imaging. Neurology 42, 527-536.

Colcombe, S.J., Erickson, K.I., Raz, N., Webb, A.G., Cohen, N.J., McAuley, E., Kramer, A.F., 2003. Aerobic fitness reduces brain tissue loss in ageing humans. J Gerontol A Biol Sci Med Sci 58, 176-180.

Courchesne, E., Chisum, H.J., Townsend, J., Cowles, A., Covington, J., Egaas, B., Harwood, M., Hinds, S., Press, G.A., 2000. Normal brain development and ageing: quantitative analysis at in vivo MR imaging in healthy volunteers. Radiology 216, 672-682.

Coyle, T.R., Kochunov, P., Patel, R.D., Nery, F.G., Lancaster, J.L., Mangin, J.F., Riviere, D., Pillow, D.R., Davis, G.J., Nicoletti, M.A., Serap Monkul, E., Fox, P.T., Soares, J.C., 2006. Cortical sulci and bipolar disorder. Neuroreport 17, 1739-1742.

Creasey, H., Rapoport, S.I., 1985. The ageing human brain. Ann Neurol 17, 2-10.

Crum, R.M., Anthony, J.C., Bassett, S.S., Folstein, M.F., 1993. Population-based norms for the Mini-Mental State Examination by age and educational level. JAMA 269, 2386-2391.

Cuenod, C.A., Bookheimer, S.Y., Hertz-Pannier, L., Zeffiro, T.A., Theodore, W.H., Le Bihan, D., 1995. Functional MRI during word generation, using conventional equipment: a potential tool for language localization in the clinical environment. Neurology 45, 1821-1827.

Curiati, P.K., Tamashiro, J.H., Squarzoni, P., Duran, F.L., Santos, L.C., Wajngarten, M., Leite, C.C., Vallada, H., Menezes, P.R., Scazufca, M., Busatto, G.F., Alves, T.C., 2009. Brain Structural Variability due to Ageing and Gender in Cognitively Healthy Elders: Results from the Sao Paulo Ageing and Health Study. AJNR Am J Neuroradiol.

Cykowski, M.D., Kochunov, P.V., Ingham, R.J., Ingham, J.C., Mangin, J.F., Riviere, D., Lancaster, J.L., Fox, P.T., 2008. Perisylvian sulcal morphology and cerebral asymmetry patterns in adults who stutter. Cereb Cortex 18, 571-583.

Dale, A.M., Fischl, B., Sereno, M.I., 1999. Cortical surface-based analysis. I. Segmentation and surface reconstruction. Neuroimage 9, 179-194.

De Leon, M.J., George, A.E., Golomb, J., Tarshish, C., Convit, A., Kluger, A., De Santi, S., McRae, T., Ferris, S.H., Reisberg, B., Ince, C., Rusinek, H., Bobinski, M., Quinn, B., Miller, D.C., Wisniewski, H.M., 1997. Frequency of hippocampal formation atrophy in normal ageing and Alzheimer's disease. Neurobiol Ageing 18, 1-11.

Dekaban, A.S., 1978. Changes in brain weights during the span of human life: relation of brain weights to body heights and body weights. Ann Neurol 4, 345-356.

Desikan, R.S., Segonne, F., Fischl, B., Quinn, B.T., Dickerson, B.C., Blacker, D., Buckner, R.L., Dale, A.M., Maguire, R.P., Hyman, B.T., Albert, M.S., Killiany, R.J., 2006. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage 31, 968-980.

Dickerson, B.C., Bakkour, A., Salat, D.H., Feczko, E., Pacheco, J., Greve, D.N., Grodstein, F., Wright, C.I., Blacker, D., Rosas, H.D., Sperling, R.A., Atri, A., Growdon, J.H., Hyman, B.T., Morris, J.C., Fischl, B., Buckner, R.L., 2009. The cortical signature of Alzheimer's disease: regionally specific cortical thinning relates to symptom severity in very mild to mild AD dementia and is detectable in asymptomatic amyloid-positive individuals. Cereb Cortex 19, 497-510.

Dickerson, B.C., Fenstermacher, E., Salat, D.H., Wolk, D.A., Maguire, R.P., Desikan, R., Pacheco, J., Quinn, B.T., Van der Kouwe, A., Greve, D.N., Blacker, D., Albert, M.S., Killiany, R.J., Fischl, B., 2008. Detection of cortical thickness correlates of cognitive performance: Reliability across MRI scan sessions, scanners, and field strengths. Neuroimage 39, 10-18.

Dow, C., Seidenberg, M., Hermann, B., 2004. Relationship between information processing speed in temporal lobe epilepsy and white matter volume. Epilepsy Behav 5, 919-925.

Duarte, A., Hayasaka, S., Du, A., Schuff, N., Jahng, G.H., Kramer, J., Miller, B., Weiner, M., 2006. Volumetric correlates of memory and executive function in normal elderly, mild cognitive impairment and Alzheimer's disease. Neurosci Lett 406, 60-65.

Dubois, J., Benders, M., Borradori-Tolsa, C., Cachia, A., Lazeyras, F., Ha-Vinh Leuchter, R., Sizonenko, S.V., Warfield, S.K., Mangin, J.F., Huppi, P.S., 2008a. Primary cortical folding in the human newborn: an early marker of later functional development. Brain 131, 2028-2041.

Dubois, J., Benders, M., Cachia, A., Lazeyras, F., Ha-Vinh Leuchter, R., Sizonenko, S.V., Borradori-Tolsa, C., Mangin, J.F., Huppi, P.S., 2008b. Mapping the early cortical folding process in the preterm newborn brain. Cereb Cortex 18, 1444-1454.

Dubois, J., Hertz-Pannier, L., Cachia, A., Mangin, J.F., Le Bihan, D., Dehaene-Lambertz, G., 2009. Structural asymmetries in the infant language and sensori-motor networks. Cereb Cortex 19, 414-423.

Duchesnay, E., Cachia, A., Roche, A., Riviere, D., Cointepas, Y., Papadopoulos-Orfanos, D., Zilbovicius, M., Martinot, J.L., Regis, J., Mangin, J.F., 2007. Classification based on cortical folding patterns. IEEE Trans Med Imaging 26, 553-565.

Fischl, B., Rajendran, N., Busa, E., Augustinack, J., Hinds, O., Yeo, B.T., Mohlberg, H., Amunts, K., Zilles, K., 2008. Cortical folding patterns and predicting cytoarchitecture. Cereb Cortex 18, 1973-1980.

Fischl, B., Sereno, M.I., Dale, A.M., 1999. Cortical surface-based analysis. II: Inflation, flattening, and a surface-based coordinate system. Neuroimage 9, 195-207.

Fischl, B., van der Kouwe, A., Destrieux, C., Halgren, E., Segonne, F., Salat, D.H., Busa, E., Seidman, L.J., Goldstein, J., Kennedy, D., Caviness, V., Makris, N., Rosen, B., Dale, A.M., 2004. Automatically parcellating the human cerebral cortex. Cereb Cortex 14, 11-22.

Fjell, A.M., Walhovd, K.B., Fennema-Notestine, C., McEvoy, L.K., Hagler, D.J., Holland, D., Brewer, J.B., Dale, A.M., 2009a. One-year brain atrophy evident in healthy ageing. J Neurosci 29, 15223-15231.

Fjell, A.M., Walhovd, K.B., Fischl, B., Reinvang, I., 2007. Cognitive function, P3a/P3b brain potentials, and cortical thickness in ageing. Hum Brain Mapp 28, 1098-1116.

Fjell, A.M., Walhovd, K.B., Reinvang, I., Lundervold, A., Salat, D., Quinn, B.T., Fischl, B., Dale, A.M., 2006. Selective increase of cortical thickness in high-performing elderly--structural indices of optimal cognitive ageing. Neuroimage 29, 984-994.

Fjell, A.M., Westlye, L.T., Amlien, I., Espeseth, T., Reinvang, I., Raz, N., Agartz, I., Salat, D.H., Greve, D.N., Fischl, B., Dale, A.M., Walhovd, K.B., 2009b. High consistency of regional cortical thinning in ageing across multiple samples. Cereb Cortex 19, 2001-2012.

Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12, 189-198.

Forn, C., Belenguer, A., Parcet-Ibars, M.A., Avila, C., 2008. Information-processing speed is the primary deficit underlying the poor performance of multiple sclerosis patients in the Paced Auditory Serial Addition Test (PASAT). J Clin Exp Neuropsychol 30, 789-796.

Fotenos, A.F., Mintun, M.A., Snyder, A.Z., Morris, J.C., Buckner, R.L., 2008. Brain volume decline in ageing: evidence for a relation between socioeconomic status, preclinical Alzheimer disease, and reserve. Arch Neurol 65, 113-120.

Fotenos, A.F., Snyder, A.Z., Girton, L.E., Morris, J.C., Buckner, R.L., 2005. Normative estimates of cross-sectional and longitudinal brain volume decline in ageing and AD. Neurology 64, 1032-1039.

Frisoni, G.B., Fox, N.C., Jack, C.R., Jr., Scheltens, P., Thompson, P.M., 2010. The clinical use of structural MRI in Alzheimer disease. Nat Rev Neurol 6, 67-77.

Genova, H.M., Hillary, F.G., Wylie, G., Rypma, B., Deluca, J., 2009. Examination of processing speed deficits in multiple sclerosis using functional magnetic resonance imaging. J Int Neuropsychol Soc 15, 383-393.

Giovanni B. Frisoni, Nick C. Fox, Clifford R. Jack Jr, Scheltens, P., Thompson, P.M., 2010. The clinical use of structural MRI in Alzheimer disease. Nature Reviews Neurology 6, 11.

Golomb, J., Kluger, A., de Leon, M.J., Ferris, S.H., Convit, A., Mittelman, M.S., Cohen, J., Rusinek, H., De Santi, S., George, A.E., 1994. Hippocampal formation size in normal human ageing: a correlate of delayed secondary memory performance. Learn Mem 1, 45-54.

Good, C.D., Johnsrude, I.S., Ashburner, J., Henson, R.N., Friston, K.J., Frackowiak, R.S., 2001. A voxel-based morphometric study of ageing in 465 normal adult human brains. Neuroimage 14, 21-36.

Graham, J.E., Rockwood, K., Beattie, B.L., Eastwood, R., Gauthier, S., Tuokko, H., McDowell, I., 1997. Prevalence and severity of cognitive impairment with and without dementia in an elderly population. Lancet 349, 1793-1796.

Greene, S.J., 2010. Neuroimaging and Neuropsychology In Ageing and Alzheimer's Disease. Boston University School of Medicine. Boston University, p. 101.

Guan, N., Tao, D., Luo, Z., Yuan, B., 2011. Non-Negative Patch Alignment Framework. IEEE Transactions on Neural Networks 22 (8), 1218-1230.

Gur, R.C., Turetsky, B.I., Matsui, M., Yan, M., Bilker, W., Hughett, P., Gur, R.E., 1999. Sex differences in brain gray and white matter in healthy young adults: correlations with cognitive performance. J Neurosci 19, 4065-4072.

Hagler, D.J., Jr., Riecke, L., Sereno, M.I., 2007. Parietal and superior frontal visuospatial maps activated by pointing and saccades. Neuroimage 35, 1562-1577.

Hagler, D.J., Jr., Sereno, M.I., 2006. Spatial maps in frontal and prefrontal cortex. Neuroimage 29, 567-577.

Hamalainen, A., Tervo, S., Grau-Olivares, M., Niskanen, E., Pennanen, C., Huuskonen, J., Kivipelto, M., Hanninen, T., Tapiola, M., Vanhanen, M., Hallikainen, M., Helkala, E.L., Nissinen, A., Vanninen, R., Soininen, H., 2007. Voxel-based morphometry to detect brain atrophy in progressive mild cognitive impairment. Neuroimage 37, 1122-1131.

Han, X., Jovicich, J., Salat, D., van der Kouwe, A., Quinn, B., Czanner, S., Busa, E., Pacheco, J., Albert, M., Killiany, R., Maguire, P., Rosas, D., Makris, N., Dale, A., Dickerson, B., Fischl, B., 2006. Reliability of MRI-derived measurements of human cerebral cortical

thickness: the effects of field strength, scanner upgrade and manufacturer. Neuroimage 32, 180-194.

He, Y., Wang, L., Zang, Y., Tian, L., Zhang, X., Li, K., Jiang, T., 2007. Regional coherence changes in the early stages of Alzheimer's disease: a combined structural and resting-state functional MRI study. Neuroimage 35, 488-500.

Hedden, T., Gabrieli, J.D., 2004. Insights into the ageing mind: a view from cognitive neuroscience. Nat Rev Neurosci 5, 87-96.

Hedden, T., Gabrieli, J.D., 2005. Healthy and pathological processes in adult development: new evidence from neuroimaging of the ageing brain. Curr Opin Neurol 18, 740-747.

Herndon RC, Lancaster JL, Giedd J, Fox PT., 1998. Quantification of white matter and gray matter volumes from 3-D magnetic resonance volume studies using fuzzy classifiers. J Magn Reson Imaging 8, 1097–1105.

Ho, B.C., Alicata, D., Ward, J., Moser, D.J., O'Leary, D.S., Arndt, S., Andreasen, N.C., 2003. Untreated initial psychosis: relation to cognitive deficits and brain morphology in first-episode schizophrenia. Am J Psychiatry 160, 142-148.

Holsinger, T., Deveau, J., Boustani, M., Williams, J.W., Jr., 2007. Does this patient have dementia? JAMA 297, 2391-2404.

Im, K., Jo, H.J., Mangin, J.F., Evans, A.C., Kim, S.I., Lee, J.M., 2010. Spatial distribution of deep sulcal landmarks and hemispherical asymmetry on the cortical surface. Cereb Cortex 20, 602-611.

Im, K., Lee, J.M., Lyttelton, O., Kim, S.H., Evans, A.C., Kim, S.I., 2008a. Brain size and cortical structure in the adult human brain. Cereb Cortex 18, 2181-2191.

Im, K., Lee, J.M., Seo, S.W., Hyung Kim, S., Kim, S.I., Na, D.L., 2008b. Sulcal morphology changes and their relationship with cortical thickness and gyral white matter volume in mild cognitive impairment and Alzheimer's disease. Neuroimage 43, 103-113.

Im, K., Lee, J.M., Seo, S.W., Yoon, U., Kim, S.T., Kim, Y.H., Kim, S.I., Na, D.L., 2008c. Variations in cortical thickness with dementia severity in Alzheimer's disease. Neurosci Lett 436, 227-231.

Im, K., Lee, J.M., Won Seo, S., Hyung Kim, S., Kim, S.I., Na, D.L., 2008d. Sulcal morphology changes and their relationship with cortical thickness and gyral white matter volume in mild cognitive impairment and Alzheimer's disease. Neuroimage 43, 103-113.

Im, K., Lee, J.M., Yoon, U., Shin, Y.W., Hong, S.B., Kim, I.Y., Kwon, J.S., Kim, S.I., 2006. Fractal dimension in human cortical surface: multiple regression analysis with cortical thickness, sulcal depth, and folding area. Hum Brain Mapp 27, 994-1003.

Jack, C.R., Jr., Petersen, R.C., O'Brien, P.C., Tangalos, E.G., 1992. MR-based hippocampal volumetry in the diagnosis of Alzheimer's disease. Neurology 42, 183-188.

Jack, C.R., Jr., Shiung, M.M., Gunter, J.L., O'Brien, P.C., Weigand, S.D., Knopman, D.S., Boeve, B.F., Ivnik, R.J., Smith, G.E., Cha, R.H., Tangalos, E.G., Petersen, R.C., 2004. Comparison of different MRI brain atrophy rate measures with clinical disease progression in AD. Neurology 62, 591-600.

Jack, C.R., Jr., Shiung, M.M., Weigand, S.D., O'Brien, P.C., Gunter, J.L., Boeve, B.F., Knopman, D.S., Smith, G.E., Ivnik, R.J., Tangalos, E.G., Petersen, R.C., 2005. Brain atrophy rates predict subsequent clinical conversion in normal elderly and amnestic MCI. Neurology 65, 1227-1231.

Jacobs, H.I., Van Boxtel, M.P., Jolles, J., Verhey, F.R., Uylings, H.B., 2011. Parietal cortex matters in Alzheimer's disease: An overview of structural, functional and metabolic findings. Neurosci Biobehav Rev.

Jernigan, T.L., Gamst, A.C., 2005. Changes in volume with age--consistency and interpretation of observed effects. Neurobiol Ageing 26, 1271-1274; discussion 1275-1278.

Jiang, T., Liu, Y., Shi, F., Shu, N., Liu, B., Jiang, J., Zhou, Y., 2008. Multimodal Magnetic Resonance Imaging for Brain Disorders: Advances and Perspectives. Brain Imaging and Behavior 2, 9.

Jouvent, E., Mangin, J.F., Porcher, R., Viswanathan, A., O'Sullivan, M., Guichard, J.P., Dichgans, M., Bousser, M.G., Chabriat, H., 2008. Cortical changes in cerebral small vessel diseases: a 3D MRI study of cortical morphology in CADASIL. Brain 131, 2201-2208.

Jouvent, E., Reyes, S., Mangin, J.F., Roca, P., Perrot, M., Thyreau, B., Herve, D., Dichgans, M., Chabriat, H., 2011. Apathy is related to cortex morphology in CADASIL. A sulcal-based morphometry study. Neurology 76, 1472-1477.

Jouvent, E., Viswanathan, A., Mangin, J.F., O'Sullivan, M., Guichard, J.P., Gschwendtner, A., Cumurciuc, R., Buffon, F., Peters, N., Pachai, C., Bousser, M.G., Dichgans, M., Chabriat, H., 2007. Brain atrophy is related to lacunar lesions and tissue microstructural changes in CADASIL. Stroke 38, 1786-1790.

Jovicich, J., Czanner, S., Han, X., Salat, D., van der Kouwe, A., Quinn, B., Pacheco, J., Albert, M., Killiany, R., Blacker, D., Maguire, P., Rosas, D., Makris, N., Gollub, R., Dale, A., Dickerson, B.C., Fischl, B., 2009. MRI-derived measurements of human subcortical, ventricular and intracranial brain volumes: Reliability effects of scan sessions, acquisition sequences, data analyses, scanner upgrade, scanner vendors and field strengths. Neuroimage 46, 177-192.

Joy, S., Kaplan, E., Fein, D., 2004. Speed and memory in the WAIS-III Digit Symbol--Coding subtest across the adult lifespan. Arch Clin Neuropsychol 19, 759-767.

Kaplan, E., 2001. *The Boston Naming Test*. Lippincott Williams Wilkins, Philadelphia.

Karas, G.B., Burton, E.J., Rombouts, S.A., van Schijndel, R.A., O'Brien, J.T., Scheltens, P., McKeith, I.G., Williams, D., Ballard, C., Barkhof, F., 2003. A comprehensive study of gray matter loss in patients with Alzheimer's disease using optimized voxel-based morphometry. Neuroimage 18, 895-907.

Keefe, R.S., Perkins, D.O., Gu, H., Zipursky, R.B., Christensen, B.K., Lieberman, J.A., 2006. A longitudinal study of neurocognitive function in individuals at-risk for psychosis. Schizophr Res 88, 26-35.

Kidd, M., 1963. Paired helical filaments in electron microscopy of Alzheimer's disease. Nature 197, 192-193.

King, R.D., Brown, B., Hwang, M., Jeon, T., George, A.T., 2010. Fractal dimension analysis of the cortical ribbon in mild Alzheimer's disease. Neuroimage.

Kochan, N.A.e.a., 2010. Effect of different impairment criteria on prevalence of "objective" mild cognitive impairment in a community sample. American Journal of Geriatric Psychiatry doi:10.1097/JGP.0b013e3181d6b6a9.

Kochunov, P., Coyle, T., Lancaster, J., Robin, D.A., Hardies, J., Kochunov, V., Bartzokis, G., Stanley, J., Royall, D., Schlosser, A.E., Null, M., Fox, P.T., 2009a. Processing speed is correlated with cerebral health markers in the frontal lobes as quantified by neuroimaging. Neuroimage.

Kochunov, P., Coyle, T., Lancaster, J., Robin, D.A., Hardies, J., Kochunov, V., Bartzokis, G., Stanley, J., Royall, D., Schlosser, A.E., Null, M., Fox, P.T., 2010. Processing speed is correlated with cerebral health markers in the frontal lobes as quantified by neuroimaging. Neuroimage 49, 1190-1199.

Kochunov, P., Mangin, J.F., Coyle, T., Lancaster, J., Thompson, P., Riviere, D., Cointepas, Y., Regis, J., Schlosser, A., Royall, D.R., Zilles, K., Mazziotta, J., Toga, A., Fox, P.T., 2005. Age-related morphology trends of cortical sulci. Hum Brain Mapp 26, 210-220.

Kochunov, P., Robin, D.A., Royall, D.R., Coyle, T., Lancaster, J., Kochunov, V., Schlosser, A.E., Fox, P.T., 2009b. Can structural MRI indices of cerebral integrity track cognitive trends in executive control function during normal maturation and adulthood? Hum Brain Mapp 30, 2581-2594.

Kochunov, P., Rogers, W., Mangin, J.F., Lancaster, J., 2011. A Library of Cortical Morphology Analysis Tools to Study Development, Ageing and Genetics of Cerebral Cortex. Neuroinformatics.

Kochunov, P., Thompson, P.M., Coyle, T.R., Lancaster, J.L., Kochunov, V., Royall, D., Mangin, J.F., Riviere, D., Fox, P.T., 2008. Relationship among neuroimaging indices of cerebral health during normal ageing. Hum Brain Mapp 29, 36-45.

Kuperberg, G.R., Broome, M.R., McGuire, P.K., David, A.S., Eddy, M., Ozawa, F., Goff, D., West, W.C., Williams, S.C., van der Kouwe, A.J., Salat, D.H., Dale, A.M., Fischl, B., 2003. Regionally localized thinning of the cerebral cortex in schizophrenia. Arch Gen Psychiatry 60, 878-888.

Lamm, C., Zelazo, P.D., Lewis, M.D., 2006. Neural correlates of cognitive control in childhood and adolescence: disentangling the contributions of age and executive function. Neuropsychologia 44, 2139-2148.

Lemaitre, H., Crivello, F., Grassiot, B., Alperovitch, A., Tzourio, C., Mazoyer, B., 2005. Age- and sex-related effects on the neuroanatomy of healthy elderly. Neuroimage 26, 900-911.

Lezak, M.D., 2004. Neuropsychological assessment (4th ed.). Oxford University Press, New York.

Li, S., Han, Y., Wang, D., Yang, H., Fan, Y., Lv, Y., Tang, H., Gong, Q., Zang, Y., He, Y., 2009. Mapping Surface Variability of the Central Sulcus in Musicians. Cereb Cortex.

Li, S., Han, Y., Wang, D., Yang, H., Fan, Y., Lv, Y., Tang, H., Gong, Q., Zang, Y., He, Y., 2010. Mapping surface variability of the central sulcus in musicians. Cereb Cortex 20, 25-33.

Li, S., Pu, F., Shi, F., Xie, S., Wang, Y., Jiang, T., 2008. Regional white matter decreases in Alzheimer's disease using optimized voxel-based morphometry. Acta Radiol 49, 84-90.

Li, S., Xia, M., Pu, F., Li, D., Fan, Y., Niu, H., Pei, B., He, Y., 2011. Age-related changes in the surface morphology of the central sulcus. Neuroimage.

Light, L.L., 1991. Memory and ageing: four hypotheses in search of data. Annu Rev Psychol 42, 333-376.

Lim, J., Choo, W.C., Chee, M.W., 2007. Reproducibility of changes in behaviour and fMRI activation associated with sleep deprivation in a working memory task. Sleep 30, 61-70.

Liu, T., Wen, W., Zhu, W., Kochan, N.A., Trollor, J.N., Reppermund, S., Jin, J.S., Luo, S., Brodaty, H., Sachdev, P.S., 2011. The relationship between cortical sulcal variability and cognitive performance in the elderly. Neuroimage.

Liu, T., Wen, W., Zhu, W., Trollor, J., Reppermund, S., Crawford, J., Jin, J.S., Luo, S., Brodaty, H., Sachdev, P., 2010. The effects of age and sex on cortical sulci in the elderly. Neuroimage 51, 19-27.

Lohmann, G., von Cramon, D.Y., Colchester, A.C., 2008. Deep sulcal landmarks provide an organizing framework for human cortical folding. Cereb Cortex 18, 1415-1420.

Luders, E., Narr, K.L., Thompson, P.M., Rex, D.E., Jancke, L., Steinmetz, H., Toga, A.W., 2004. Gender differences in cortical complexity. Nat Neurosci 7, 799-800.

Luft, F.C., Fineberg, N.S., Miller, J.Z., Rankin, L.I., Grim, C.E., Weinberger, M.H., 1980. The effects of age, race and heredity on glomerular filtration rate following volume expansion and contraction in normal man. Am J Med Sci 279, 15-24.

Magnotta, V.A., Andreasen, N.C., Schultz, S.K., Harris, G., Cizadlo, T., Heckel, D., Nopoulos, P., Flaum, M., 1999. Quantitative in vivo measurement of gyrification in the human brain: changes associated with ageing. Cereb Cortex 9, 151-160.

Mangin, J.-F., 2000. Entropy minimization for automatic correction of intensity non uniformity. Hilton Head Island, SC: IEEE Press, 8.

Mangin, J., Frouin, V., Bloch, I., Régis, J., López-Krahe, J., 1995a. From 3D Magnetic Resonance Images to Structural Representations of the Cortex Topography Using Topology Preserving Deformations. J Math Imaging Vis 5, 21.

Mangin, J.F., Jouvent, E., Cachia, A., 2010. In-vivo measurement of cortical morphology: means and meanings. Curr Opin Neurol 23, 359-367.

Mangin, J.F., Poupon, C., Cointepas, Y., Riviere, D., Papadopoulos-Orfanos, D., Clark, C.A., Regis, J., Le Bihan, D., 2002. A framework based on spin glass models for the inference of anatomical connectivity from diffusion-weighted MR data - a technical review. NMR Biomed 15, 481-492.

Mangin, J.F., Riviere, D., Cachia, A., Duchesnay, E., Cointepas, Y., Papadopoulos-Orfanos, D., Scifo, P., Ochiai, T., Brunelle, F., Regis, J., 2004. A framework to study the cortical folding patterns. Neuroimage 23 Suppl 1, S129-138.

Mangin, J.F., Tupin, F., Frouin, V., Bloch, I., Rougetet, R., Regis, J., Lopezkrahe, J., 1995b. Deformable topological models for segmentation of 3D medical images. Information Processing in Medical Imaging 3, 153-164.

Mangin, J.F., Tupin, F., Frouin, V., Bloch, I., Rougetet, R., Regis, J., Lopezkrahe, J., 1995c. Deformable topological models for segmentation of 3D medical images. Information Processing in Medical Imaging 3, 153-164, 408.

Marcus, D.S., Fotenos, A.F., Csernansky, J.G., Morris, J.C., Buckner, R.L., 2010. Open access series of imaging studies: longitudinal MRI data in nondemented and demented older adults. J Cogn Neurosci 22, 2677-2684.

Marcus, D.S., Wang, T.H., Parker, J., Csernansky, J.G., Morris, J.C., Buckner, R.L., 2007. Open Access Series of Imaging Studies (OASIS): cross-sectional MRI data in young, middle aged, nondemented, and demented older adults. J Cogn Neurosci 19, 1498-1507.

Markowitsch, H.J., 1995. Which brain regions are critically involved in the retrieval of old episodic memory? Brain Res Brain Res Rev 21, 117-127.

Marlet, J.J., 1983. [The thickness of the frontal bone and its relation to cranial hyperostosis]. Ned Tijdschr Geneeskd 127, 1049-1051.

Marshall, J.C., Fink, G.R., 2001. Spatial cognition: where we were and where we are. Neuroimage 14, S2-7.

Martinussen, M., Fischl, B., Larsson, H.B., Skranes, J., Kulseng, S., Vangberg, T.R., Vik, T., Brubakk, A.M., Haraldseth, O., Dale, A.M., 2005. Cerebral cortex thickness in 15-year-old adolescents with low birth weight measured by an automated MRI-based method. Brain 128, 2588-2596.

Mega, M.S., Thompson, P.M., Cummings, J.L., Back, C.L., Xu, M.L., Zohoori, S., Goldkorn, A., Moussai, J., Fairbanks, L., Small, G.W., Toga, A.W., 1998. Sulcal variability in the Alzheimer's brain: correlations with cognition. Neurology 50, 145-151.

Miller, A.K., Alston, R.L., Corsellis, J.A., 1980. Variation with age in the volumes of grey and white matter in the cerebral hemispheres of man: measurements with an image analyser. Neuropathol Appl Neurobiol 6, 119-132.

Miller, E.K., Cohen, J.D., 2001. An integrative theory of prefrontal cortex function. Annu Rev Neurosci 24, 167-202.

Molenberghs, P., Brander, C., Mattingley, J.B., Cunnington, R., 2010. The role of the superior temporal sulcus and the mirror neuron system in imitation. Hum Brain Mapp.

Molko, N., Cachia, A., Riviere, D., Mangin, J.F., Bruandet, M., Le Bihan, D., Cohen, L., Dehaene, S., 2003. Functional and structural alterations of the intraparietal sulcus in a developmental dyscalculia of genetic origin. Neuron 40, 847-858.

Morris, J.C., 1993. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology 43, 2412-2414.

Morris, J.C., Storandt, M., Miller, J.P., McKeel, D.W., Price, J.L., Rubin, E.H., Berg, L., 2001. Mild cognitive impairment represents early-stage Alzheimer disease. Arch Neurol 58, 397-405.

Morrison, J.H., Hof, P.R., 1997. Life and death of neurons in the ageing brain. Science 278, 412-419.

Morrison, J.H., Hof, P.R., 2002. Selective vulnerability of corticocortical and hippocampal circuits in ageing and Alzheimer's disease. Prog Brain Res 136, 467-486.

Morrison, J.H., Hof, P.R., 2007. Life and death of neurons in the ageing cerebral cortex. Int Rev Neurobiol 81, 41-57.

Murphy, E.A., Holland, D., Donohue, M., McEvoy, L.K., Hagler, D.J., Jr., Dale, A.M., Brewer, J.B., 2010. Six-month atrophy in MTL structures is associated with subsequent memory decline in elderly controls. Neuroimage.

Narr, K.L., Woods, R.P., Thompson, P.M., Szeszko, P., Robinson, D., Dimtcheva, T., Gurbani, M., Toga, A.W., Bilder, R.M., 2007. Relationships between IQ and regional cortical gray matter thickness in healthy adults. Cereb Cortex 17, 2163-2171.

Newman, L.M., Trivedi, M.A., Bendlin, B.B., Ries, M.L., Johnson, S.C., 2007. The Relationship Between Gray Matter Morphometry and Neuropsychological Performance in a Large Sample of Cognitively Healthy Adults. Brain Imaging Behav 1, 3-10.

Nopoulos, P., Flaum, M., O'Leary, D., Andreasen, N.C., 2000. Sexual dimorphism in the human brain: evaluation of tissue volume, tissue composition and surface anatomy using magnetic resonance imaging. Psychiatry Res 98, 1-13.

Nordahl, C.W., Dierker, D., Mostafavi, I., Schumann, C.M., Rivera, S.M., Amaral, D.G., Van Essen, D.C., 2007. Cortical folding abnormalities in autism revealed by surface-based morphometry. J Neurosci 27, 11725-11735.

O'Sullivan, M., Jones, D.K., Summers, P.E., Morris, R.G., Williams, S.C., Markus, H.S., 2001. Evidence for cortical "disconnection" as a mechanism of age-related cognitive decline. Neurology 57, 632-638.

Panizzon, M.S., Fennema-Notestine, C., Eyler, L.T., Jernigan, T.L., Prom-Wormley, E., Neale, M., Jacobson, K., Lyons, M.J., Grant, M.D., Franz, C.E., Xian, H., Tsuang, M., Fischl, B., Seidman, L., Dale, A., Kremen, W.S., 2009. Distinct genetic influences on cortical surface area and cortical thickness. Cereb Cortex 19, 2728-2735.

Park, D.C., Reuter-Lorenz, P., 2009. The adaptive brain: ageing and neurocognitive scaffolding. Annu Rev Psychol 60, 173-196.

Peers, P.V., Ludwig, C.J., Rorden, C., Cusack, R., Bonfiglioli, C., Bundesen, C., Driver, J., Antoun, N., Duncan, J., 2005. Attentional functions of parietal and frontal cortex. Cereb Cortex 15, 1469-1484.

Penttilä, J., Cachia, A., Martinot, J.-L., 2009. Cortical folding difference between patients with early-onset and patients with intermediate-onset bipolar disorder. Bipolar Disorder 11.

Penttila, J., Paillere-Martinot, M.L., Martinot, J.L., Mangin, J.F., Burke, L., Corrigall, R., Frangou, S., Cachia, A., 2008. Global and Temporal Cortical Folding in Patients With Early-Onset Schizophrenia. J Am Acad Child Adolesc Psychiatry.

Penttila, J., Paillere-Martinot, M.L., Martinot, J.L., Ringuenet, D., Wessa, M., Houenou, J., Gallarda, T., Bellivier, F., Galinowski, A., Bruguiere, P., Pinabel, F., Leboyer, M., Olie, J.P., Duchesnay, E., Artiges, E., Mangin, J.F., Cachia, A., 2009. Cortical folding in patients with bipolar disorder or unipolar depression. J Psychiatry Neurosci 34, 127-135.

Raz, N., Gunning-Dixon, F., Head, D., Rodrigue, K.M., Williamson, A., Acker, J.D., 2004. Ageing, sexual dimorphism, and hemispheric asymmetry of the cerebral cortex: replicability of regional differences in volume. Neurobiol Ageing 25, 377-396.

Raz, N., Lindenberger, U., Rodrigue, K.M., Kennedy, K.M., Head, D., Williamson, A., Dahle, C., Gerstorf, D., Acker, J.D., 2005. Regional brain changes in ageing healthy adults: general trends, individual differences and modifiers. Cereb Cortex 15, 1676-1689.

Raz, N., Rodrigue, K.M., 2006. Differential ageing of the brain: patterns, cognitive correlates and modifiers. Neurosci Biobehav Rev 30, 730-748.

Reitan, R.M., Wolfson, D., 1994. A selective and critical review of neuropsychological deficits and the frontal lobes. Neuropsychol Rev 4, 161-198.

Reitan, R.M., Wolfson, D, 1985. The Halstead-Reitan Neuropsycholgical Test Battery: Theory and clinical interpretation. Neuropsychological Press, Tucson, AZ.

Resnick, S.M., Pham, D.L., Kraut, M.A., Zonderman, A.B., Davatzikos, C., 2003. Longitudinal magnetic resonance imaging studies of older adults: a shrinking brain. J Neurosci 23, 3295-3301.

Rettmann, M.E., Kraut, M.A., Prince, J.L., Resnick, S.M., 2006. Cross-sectional and longitudinal analyses of anatomical sulcal changes associated with ageing. Cereb Cortex 16, 1584-1594.

Rey, A., 1964. L'examen clinique en psychologie. Presses Universitaires de France, Paris.

Riviere, D., Mangin, J.F., Papadopoulos-Orfanos, D., Martinez, J.M., Frouin, V., Regis, J., 2002. Automatic recognition of cortical sulci of the human brain using a congregation of neural networks. Med Image Anal 6, 77-92.

Rogan, S., Lippa, C.F., 2002. Alzheimer's disease and other dementias: a review. Am J Alzheimers Dis Other Demen 17, 11-17.

Rosas, H.D., Liu, A.K., Hersch, S., Glessner, M., Ferrante, R.J., Salat, D.H., van der Kouwe, A., Jenkins, B.G., Dale, A.M., Fischl, B., 2002. Regional and progressive thinning of the cortical ribbon in Huntington's disease. Neurology 58, 695-701.

Rowe, A.D., Bullock, P.R., Polkey, C.E., Morris, R.G., 2001. "Theory of mind" impairments and their relationship to executive functioning following frontal lobe excisions. Brain 124, 600-616.

Rowe, J.B., Sakai, K., Lund, T.E., Ramsoy, T., Christensen, M.S., Baare, W.F., Paulson, O.B., Passingham, R.E., 2007. Is the prefrontal cortex necessary for establishing cognitive sets? J Neurosci 27, 13303-13310.

Rypma, B., Eldreth, D.A., Rebbechi, D., 2007. Age-related differences in activation-performance relations in delayed-response tasks: a multiple component analysis. Cortex 43, 65-76.

Sachdev, P.S., Brodaty, H., Reppermund, S., Kochan, N.A., Trollor, J.N., Draper, B., Slavin, M.J., Crawford, J., Kang, K., Broe, G.A., Mather, K.A., Lux, O., 2010. The Sydney Memory and Ageing Study (MAS): methodology and baseline medical and neuropsychiatric characteristics of an elderly epidemiological non-demented cohort of Australians aged 70-90 years. Int Psychogeriatr, 1-17.

Said, C.P., Moore, C.D., Engell, A.D., Todorov, A., Haxby, J.V., 2010. Distributed representations of dynamic facial expressions in the superior temporal sulcus. J Vis 10.

Salat, D.H., Buckner, R.L., Snyder, A.Z., Greve, D.N., Desikan, R.S., Busa, E., Morris, J.C., Dale, A.M., Fischl, B., 2004. Thinning of the cerebral cortex in ageing. Cereb Cortex 14, 721-730.

Salat, D.H., Greve, D.N., Pacheco, J.L., Quinn, B.T., Helmer, K.G., Buckner, R.L., Fischl, B., 2009. Regional white matter volume differences in nondemented ageing and Alzheimer's disease. Neuroimage 44, 1247-1258.

Salthouse, T.A., 1996. The processing-speed theory of adult age differences in cognition. Psychol Rev 103, 403-428.

Sanchez-Benavides, G., Gomez-Anson, B., Molinuevo, J.L., Blesa, R., Monte, G.C., Buschke, H., Pena-Casanova, J., 2010. Medial temporal lobe correlates of memory screening measures in normal ageing, MCI, and AD. J Geriatr Psychiatry Neurol 23, 100-108.

Scahill, R.I., Frost, C., Jenkins, R., Whitwell, J.L., Rossor, M.N., Fox, N.C., 2003. A longitudinal study of brain volume changes in normal ageing using serial registered magnetic resonance imaging. Arch Neurol 60, 989-994.

Seo, S.W., Im, K., Lee, J.M., Kim, S.T., Ahn, H.J., Go, S.M., Kim, S.H., Na, D.L., 2009. Effects of demographic factors on cortical thickness in Alzheimer's disease. Neurobiol Ageing.

Seong, J.K., Im, K., Yoo, S.W., Seo, S.W., Na, D.L., Lee, J.M., 2010. Automatic extraction of sulcal lines on cortical surfaces based on anisotropic geodesic distance. Neuroimage 49, 293-302.

Sereno, M.I., Huang, R.S., 2006. A human parietal face area contains aligned head-centered visual and tactile maps. Nat Neurosci 9, 1337-1343.

Shi, F., Liu, B., Zhou, Y., Yu, C., Jiang, T., 2009. Hippocampal volume and asymmetry in mild cognitive impairment and Alzheimer's disease: Meta-analyses of MRI studies. Hippocampus 19, 1055-1064.

Sluimer, J.D., van der Flier, W.M., Karas, G.B., Fox, N.C., Scheltens, P., Barkhof, F., Vrenken, H., 2008. Whole-brain atrophy rate and cognitive decline: longitudinal MR study of memory clinic patients. Radiology 248, 590-598.

Small, G.W., Siddarth, P., Burggren, A.C., Kepe, V., Ercoli, L.M., Miller, K.J., Lavretsky, H., Thompson, P.M., Cole, G.M., Huang, S.C., Phelps, M.E., Bookheimer, S.Y., Barrio, J.R., 2009. Influence of cognitive status, age, and APOE-4 genetic risk on brain FDDNP positron-emission tomography imaging in persons without dementia. Arch Gen Psychiatry 66, 81-87.

Smith, C.D., Chebrolu, H., Wekstein, D.R., Schmitt, F.A., Markesbery, W.R., 2007. Age and gender effects on human brain anatomy: a voxel-based morphometric study in healthy elderly. Neurobiol Ageing 28, 1075-1087.

Sowell, E.R., Peterson, B.S., Kan, E., Woods, R.P., Yoshii, J., Bansal, R., Xu, D., Zhu, H., Thompson, P.M., Toga, A.W., 2007. Sex differences in cortical thickness mapped in 176 healthy individuals between 7 and 87 years of age. Cereb Cortex 17, 1550-1560.

Sowell, E.R., Peterson, B.S., Thompson, P.M., Welcome, S.E., Henkenius, A.L., Toga, A.W., 2003. Mapping cortical change across the human life span. Nat Neurosci 6, 309-315.

Sowell, E.R., Thompson, P.M., Leonard, C.M., Welcome, S.E., Kan, E., Toga, A.W., 2004. Longitudinal mapping of cortical thickness and brain growth in normal children. J Neurosci 24, 8223-8231.

Sowell, E.R., Thompson, P.M., Rex, D., Kornsand, D., Tessner, K.D., Jernigan, T.L., Toga, A.W., 2002. Mapping sulcal pattern asymmetry and local cortical surface gray matter distribution in vivo: maturation in perisylvian cortices. Cereb Cortex 12, 17-26.

Sowell, E.R., Thompson, P.M., Tessner, K.D., Toga, A.W., 2001. Mapping continued brain growth and gray matter density reduction in dorsal frontal cortex: Inverse relationships during postadolescent brain maturation. J Neurosci 21, 8819-8829.

Spreen, O., Benton, A.L. , 1969. Neurosensory Center Comprehensive Examination for Aphasia: Manual of instructions (NCCEA). University of Victoria, Victoria, BC.

Steen, R.G., Gronemeyer, S.A., Taylor, J.S., 1995. Age-related changes in proton T1 values of normal human brain. J Magn Reson Imaging 5, 43-48.

Stonnington, C.M., Tan, G., Kloppel, S., Chu, C., Draganski, B., Jack, C.R., Jr., Chen, K., Ashburner, J., Frackowiak, R.S., 2008. Interpreting scan data acquired from multiple scanners: a study with Alzheimer's disease. Neuroimage 39, 1180-1185.

Strauss, E., Sherman, E.M.S., Spreen, O., 2006. A Compendium of neuropsychological tests: Administration, norms, and commentary (3rd ed.). Oxford University Press, New York.

Sumerall, S.W., Timmons, P.L., James, A.L., Ewing, M.J., Oehlert, M.E., 1997. Expanded norms for the Controlled Oral Word Association Test. J Clin Psychol 53, 517-521.

Symonds, L.L., Archibald, S.L., Grant, I., Zisook, S., Jernigan, T.L., 1999. Does an increase in sulcal or ventricular fluid predict where brain tissue is lost? J Neuroimaging 9, 201-209.

Tao, D., Li, X., Wu X., Maybank J.S., 2009. Geometric Mean for Subspace Selection. IEEE Trans. Pattern Anal. Mach. Intell. 31(2), 260-274.

Tao, D., Li, X., Wu X., Maybank J.S., 2007. General Tensor Discriminant Analysis and Gabor Features for Gait Recognition. IEEE Trans. Pattern Anal. Mach. Intell. 29(10), 1700-1715.

Terry, R.D., 1963. The Fine Structure of Neurofibrillary Tangles in Alzheimer's Disease. J Neuropathol Exp Neurol 22, 629-642.

Terry, R.D., DeTeresa, R., Hansen, L.A., 1987. Neocortical cell counts in normal human adult ageing. Ann Neurol 21, 530-539.

Thompson, P., Toga, A.W., 1996. A surface-based technique for warping three-dimensional images of the brain. IEEE Trans Med Imaging 15, 402-417.

Thompson, P.M., Hayashi, K.M., de Zubicaray, G., Janke, A.L., Rose, S.E., Semple, J., Herman, D., Hong, M.S., Dittmer, S.S., Doddrell, D.M., Toga, A.W., 2003. Dynamics of gray matter loss in Alzheimer's disease. J Neurosci 23, 994-1005.

Thompson, P.M., Moussai, J., Zohoori, S., Goldkorn, A., Khan, A.A., Mega, M.S., Small, G.W., Cummings, J.L., Toga, A.W., 1998. Cortical variability and asymmetry in normal ageing and Alzheimer's disease. Cereb Cortex 8, 492-509.

Tisserand, D.J., van Boxtel, M.P., Pruessner, J.C., Hofman, P., Evans, A.C., Jolles, J., 2004. A voxel-based morphometric study to determine individual differences in gray matter density associated with age and cognitive change over time. Cereb Cortex 14, 966-973.

Tisserand, D.J., Visser, P.J., van Boxtel, M.P., Jolles, J., 2000. The relation between global and limbic brain volumes on MRI and cognitive performance in healthy individuals across the age range. Neurobiol Ageing 21, 569-576.

Tomlinson, B.E., Blessed, G., Roth, M., 1968. Observations on the brains of non-demented old people. J Neurol Sci 7, 331-356.

Toro, R., Perron, M., Pike, B., Richer, L., Veillette, S., Pausova, Z., Paus, T., 2008. Brain size and folding of the human cerebral cortex. Cereb Cortex 18, 2352-2357.

Turken, A., Whitfield-Gabrieli, S., Bammer, R., Baldo, J.V., Dronkers, N.F., Gabrieli, J.D., 2008. Cognitive processing speed and the structure of white matter pathways: convergent evidence from normal variation and lesion studies. Neuroimage 42, 1032-1044.

Van Essen, D.C., 1997. A tension-based theory of morphogenesis and compact wiring in the central nervous system. Nature 385, 313-318.

Van Pelt, J., van Ooyen, A., Uylings, H.B., 2001. The need for integrating neuronal morphology databases and computational environments in exploring neuronal structure and function. Anat Embryol (Berl) 204, 255-265.

Van Petten, C., 2004. Relationship between hippocampal volume and memory ability in healthy individuals across the lifespan: review and meta-analysis. Neuropsychologia 42, 1394-1413.

Van Petten, C., Plante, E., Davidson, P.S., Kuo, T.Y., Bajuscak, L., Glisky, E.L., 2004. Memory and executive function in older adults: relationships with temporal and prefrontal gray matter volumes and white matter hyperintensities. Neuropsychologia 42, 1313-1335.

Vigneau, M., Beaucousin, V., Herve, P.Y., Duffau, H., Crivello, F., Houde, O., Mazoyer, B., Tzourio-Mazoyer, N., 2006. Meta-analyzing left hemisphere language areas: phonology, semantics, and sentence processing. Neuroimage 30, 1414-1432.

Wechsler, D., 1981. Wechsler Adult Intelligence Scale-- Revised (WAIS-R). Psychological Corporation; Harcourt, Brace, Jovanovich., San Antonio, TX.

Wechsler, D., 1997a. Wechsler Adult Intelligence Scale-- Version III (WAIS-III). Psychological Corporation; Harcourt Brace & Co., San Antonio, TX.

Wechsler, D., 1997b. Wechsler Memory Scale--Version III (WMS-III). Psychological Corporation; Harcourt Brace & Co., San Antonio, TX.

Welker, W., 1988. Why does cerebral cortex fissure and fold? A review of determinants of gyri and sulci. Cerebral Cortex 8, 132.

Wen, W., Sachdev, P.S., Chen, X., Anstey, K., 2006. Gray matter reduction is correlated with white matter hyperintensity volume: a voxel-based morphometric study in a large epidemiological sample. Neuroimage 29, 1031-1039.

Whitwell, J.L., Przybelski, S.A., Weigand, S.D., Knopman, D.S., Boeve, B.F., Petersen, R.C., Jack, C.R., Jr., 2007. 3D maps from multiple MRI illustrate changing atrophy patterns as subjects progress from mild cognitive impairment to Alzheimer's disease. Brain 130, 1777-1786.

Wimo, A., Jonsson, L., Winblad, B., 2006. An estimate of the worldwide prevalence and direct costs of dementia in 2003. Dement Geriatr Cogn Disord 21, 175-181.

Xu, J., Kobayashi, S., Yamaguchi, S., Iijima, K., Okada, K., Yamashita, K., 2000. Gender effects on age-related changes in brain structure. AJNR Am J Neuroradiol 21, 112-118.

Yankner, B.A., Lu, T., Loerch, P., 2008. The ageing brain. Annu Rev Pathol 3, 41-66.

Zheng, Z.Z., Wild, C., Trang, H.P., 2010. Spatial organization of neurons in the superior temporal sulcus. J Neurosci 30, 1201-1203.

Ziegler, D.A., Piguet, O., Salat, D.H., Prince, K., Connally, E., Corkin, S., 2008. Cognition in healthy ageing is related to regional white matter integrity, but not cortical thickness. Neurobiol Ageing.

Zilles, K., Armstrong, E., Schleicher, A., Kretschmann, H.J., 1988. The human pattern of gyrification in the cerebral cortex. Anat Embryol (Berl) 179, 173-179.