NeuroImage 46 (2009) 257–269

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Cognitive function and brain structure correlations in healthy elderly East Asians

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ARTICLE INFO

Article history:
Received 16 October 2008
Revised 15 December 2008
Accepted 22 January 2009
Available online 3 February 2009

Keywords:
Cognitive aging
Cohort studies
MRI
Volumetry
Cortical thickness
White matter

ABSTRACT

We investigated the effect of age and health variables known to modulate cognitive aging on several measures of cognitive performance and brain volume in a cohort of healthy, non-demented persons of Chinese descent aged between 55 and 86 years. 248 subjects contributed combined neuropsychological, MR imaging, health and socio-demographic information. Speed of processing showed the largest age-related decline. Education and plasma homocysteine levels modulated age-related decline in cognitive performance. Total cerebral volume declined at an annual rate of 0.4%/yr. Gray and white matter volume loss was comparable in magnitude. Regionally, there was relatively greater volume loss in the lateral prefrontal cortex bilaterally, around the primary visual cortex as well as bilateral superior parietal cortices. Speed of processing showed significant positive correlation with gray matter volume in several frontal, parietal and midline occipital regions bilaterally. In spite of differences in diet, lifestyle and culture, these findings are broadly comparable to studies conducted in Caucasian populations and suggest generalizability of processes involved in age-related decline in cognition and brain volume.

Introduction

Maintaining optimal cognitive function for as long as possible is a vital element of successful aging (Rowe and Kahn, 1987) and this goal has motivated many cognitive and imaging studies of brain aging. With possibly one exception (Mu et al., 1999) all such studies have been conducted in predominantly Caucasian populations (Carlson et al., 2008; Fotenos et al., 2005; Prins et al., 2002; Raz et al., 1998; Resnick et al., 2003; Scahill et al., 2003).

As the additional resources needed to care for disabled elderly could significantly compound the pressure exerted on global energy and food availability, there is an urgent need for accurate information about brain and cognitive aging among Asians — who constitute the most rapidly aging population grouping in the world. To illustrate, in 1982, adults over the age of 65 years represented only 4.9% of the Chinese population (Liang et al., 1985). This increased to 6.96% of 1.3 billion in 2000 (National Bureau of Statistics People's Republic of China, 2001), and could rise to 23.7% of 1.4 billion in 2050 (Population division of the department of economic and social affairs of the United Nations Secretariat, 2007) i.e. equivalent to the entire United States population in 2006.

The rate of cognitive decline and brain atrophy can be influenced by education (Staff et al., 2004) as well as a variety of cardiovascular risk/fitness factors (Colcombe et al., 2004; Murray et al., 2005; Raz et al., 2003a) in ways that probably generalize across populations. However, diet (Kalmijn et al., 2004; Mattson, 2003), environmental factors and genetic makeup differ across ethnic groups and could affect the aging process (Bamshad, 2005; Kirkwood, 2005). Additionally, culture has been shown to influence cognition (Nisbett and Miyamoto, 2005; Park and Gutchess, 2002) and modulate task-related brain activation (Goh et al., 2007).

Comparing rates of change of brain volume across aging studies requires attention to differences in image acquisition and quality control (Littmann et al., 2006; Preboske et al., 2006), sample size and age span of the cohort (Fotenos et al., 2005; Jernigan and Gamst, 2005), health of volunteers (Resnick et al., 2003), image measurement technique (Gunter et al., 2003) and method of correction for differences in head size (Buckner et al., 2004). The range in findings across studies makes it difficult to assess what is 'normal' for a particular group or to judge the benefit of environmental modifiers or the efficacy of interventions that could reduce the impact of age-related change in cognition. These challenges are compounded by the fact that excellent imaging data may not be accompanied by detailed neuropsychological testing or associated health information and vice versa. Such practical realities have motivated the formation of multi-laboratory consortiums to standardize data collection (Jack et al., 2008; Mueller et al., 2005), so as to afford the establishment of baseline data that has robust clinical utility.

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doi:10.1016/j.neuroimage.2009.01.036

In recognition of the methodological issues that could confound the interpretation of contemporary structural imaging studies, we report cross-sectional data originating from a large (248 subjects), single-centre, longitudinal aging study that incorporated recent advancements in image acquisition, quality control (Mallozzi et al., 2006, 2004), image processing (Jovicich et al., 2006) and analysis (Desikan et al., 2006; Fischl et al., 2004) techniques.

We focused on a 'post-retirement' age range of 55–86 years, instead of attempting to characterize lifespan changes, because age-related changes in cognition have the greatest economic and societal impact in this segment of the population. In addition to age, we evaluated other factors that could affect cognitive performance (Enzinger et al., 2005). We obtained a number of measures of brain structure and evaluated the effect of age and health variables of interest on these measures. Mindful that pre-existing chronic illness can influence imaging findings (Resnick et al., 2003) we *prospectively* selected volunteers who met strict health criteria in order that our results would represent a standard an average middle class East Asian individual could benchmark against. Finally, we correlated measures of cognitive performance and brain structure. In view of the increasing automation in brain structure measurement, we made head-to-head comparisons between manual and semi-automated measurements of three commonly reported brain measures as a preface to more extensive data analysis using this methodology. This cross sectional data, while primarily descriptive and comparative in nature, should provide a valuable starting point from which to base future studies concerning brain aging in Asians.

Methods

Participants

The volunteers were members of the Singapore Longitudinal Aging Brain Study, a community-based epidemiologic study involving healthy elderly volunteers that sought to characterize age-related brain changes and cognitive performance in persons of Chinese descent resident in Singapore. The study was approved by the Singapore General Hospital Institutional Review Board and participants gave informed consent prior to undergoing evaluation.

349 healthy adults participated in the first wave of the study; data from 248 volunteers are reported here. 285 of the participants were recruited through newspaper advertisements and from active aging clubs. The remaining 64 volunteers were participants from a separate community-based longitudinal aging study who agreed to undergo neuroimaging. All participants were screened in a telephone interview before undergoing a structured interview at the laboratory.

Participants were persons aged 55 years and above with no known active medical conditions other than treated, uncomplicated diabetes mellitus or hypertension. Participants were excluded if they had any of the following: (1) history of significant vascular events (i.e., myocardial infarction, stroke or peripheral vascular disease); (2) history of malignant neoplasia of any form; (3) a history of cardiac, lung, liver, or kidney failure; (4) active or inadequately treated thyroid disease; (5) active neurological or psychiatric conditions; (6) a history of head trauma with loss of consciousness; (7) a Mini-Mental State Examination (MMSE) (Folstein et al., 1975) score <26; (8) a 15-point modified-Geriatric Depression Screening Scale (GDS) (Sheikh and Yesavage, 1986) score >9; or (9) a history of illicit substance use. Participants could be excluded on the basis of disqualifying information obtained during the structured interview, results of blood tests, or self-reports of medication and supplement intake.

Blood tests

Venous blood samples were drawn between 8:30 am and 9:30 am after an overnight fast and tested for the following: APOE genotype, total fasting glucose level, total fasting cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, cholesterol/HDL ratio, C-reactive protein, homocysteine, folate, and vitamin B12. Measurements were made at the National University Hospital Laboratory using quality-controlled procedures.

Neuropsychological assessment

Participants were assessed between 10 am and 2 pm, within 3 months of undergoing MR imaging by trained researchers who worked under the supervision of a clinical neuropsychologist. A battery of 11 neuropsychological tests evaluating six cognitive domains — attention, verbal memory, visuospatial memory, executive functioning, speed of processing, and language was used. We minimized the effects of language and culture by using tests that contained items that were relatively familiar to the study population. Attention was assessed using the Digit Span subtest from the Wechsler Memory Scale III (Wechsler, 1997) and a computerized version of a Spatial Span task. Verbal memory was evaluated using the Rey Auditory Verbal Learning Test (RAVLT) (Lezak et al., 2004) and a Verbal-Paired Associates test. Visuospatial memory was evaluated using the Visual Reproduction (VR) subtest from the WMS-III and a Visual Paired Associates test. Executive functioning was assessed using a Categorical Verbal Fluency test (using categories of animals, vegetables and fruits), the Design Fluency test (Delis et al., 2001), and the Trail Making Test B (Reitan and Wolfson, 1985). Speed of processing was assessed with the Trail-Making Test A (Reitan and Wolfson, 1985) and the Symbol-Digit Modalities Test (SDMT) (Smith, 1991). Language was evaluated using the Object and Action Naming Battery (Druks and Masterson, 2000). The tests were administered in either English or Mandarin according to the subject's most proficient language. The individual test scores were standardized (z-transformed) and combined into six theoretically motivated composite scores (attention, verbal memory, visuospatial memory, speed of processing, executive functions and language) to limit the number of comparisons.

MR imaging

MRI was performed on a 3T Siemens Allegra (Siemens, Erlangen, Germany) system using a standardized imaging procedure that incorporated a number of quality control measures. Each day, following thermal stabilization of the MR system, a 165-sphere phantom (The Phantom Laboratory, Salem, NY) was scanned to evaluate geometric distortion and signal to noise ratio (Mallozzi et al., 2006). The same gradient system and 4-channel head coil were used throughout the study.

Participants were carefully positioned in the magnet to lie within the centre of the spherical 22 cm 'sweet spot' of the head coil. Participants whose necks were short or whose heads were too large to fulfill this requirement were excluded from the data analyses. Participants were instructed to have their usual amount of liquid prior to scanning in order to minimize the effect of hydration status on brain volume (Duning et al., 2005). To minimize the requirement for a post-hoc image reorientation, we acquired high-resolution sagittal T1-weighted images keeping the long axis of the left hippocampus parallel to the imaging volume.

The T1-weighted MP-RAGE sequence used for morphometric analysis provided excellent gray-white matter contrast as well as gray matter-cerebrospinal fluid contrast. It was identical to that used by the Alzheimer's Disease Neuroimaging Initiative ADNI consortium (Jack et al., 2008). (TR = 2300 ms, TI = 900 ms, flip angle = 9°, BW 240 Hz/pixel, FOV 256 × 240 mm, Matrix 256 × 256; resulting voxel dimensions: 1.0 × 1.0 × 1.1 mm, Acquisition time 9 min 14sec). Parallel imaging was used to improve the signal-to-noise ratio instead of shortening the scan time — we obtained a single high-quality image

instead of averaging two or more rapidly-acquired images. Images were inspected for motion artifact at the time of acquisition and scanning was repeated as necessary. The resultant images underwent non-uniformity correction (Sled et al., 1998) and 3D-gradient unwarping (Jovicich et al., 2006) to correct for any geometric distortions arising from gradient non-linearity.

2D-FLAIR images obtained in the axial plane (TR = 10,000 ms, TI = 2500 ms, TE = 96 ms, voxel dimensions 0.9 × 0.9 × 5.0 mm) were used to evaluate for silent infarcts and to measure the volume of white matter hyperintensities (not reported here). A neurologist reviewed images showing potential pathological features or variants.

After the aforementioned exclusion criteria were met and images were evaluated for quality, 248 complete sets of demographic, health, MR imaging and neuropsychological data were subject to further analysis.

MR image analysis

A standardized MRI data-processing pipeline was used to process the data. Both manual and semi-automated measurements were made (for brevity — the use of the semi-automatic methods will be referred to as 'automated measures'). Manual, interactive volumetry was performed for Total Intracranial Volume (TIV), Hippocampus (HC), and ventricle volume by two trained researchers using Analyze 7.0 (Mayo Clinic, Rochester MN) on graphic tablets (Wacom DTU-710, Wacom Saitama, Japan). The automated volume measurements were performed using FreeSurfer 3.0.5 (http://surfer.nmr.mgh.harvard.edu/; Martinos Imaging Centre, Charlestown MA).

Manual measurements

Hippocampal volumes. The 3D T1-weighted sagittal images were first re-oriented in the coronal plane, orthogonal to the principal axis of the hippocampal (HC) formation. Images were enlarged by 4× and re-sampled using cubic spline interpolation. The landmarks used for tracing have been previously described (Jack et al., 1998, 1989; Watson et al., 1992) but see Supplementary Fig. 1 for some exemplars. Orthogonal views of the hippocampus were used to facilitate tracing. The first slice traced was one in which the crura of the fornices could be seen enface. Coronal images of the hippocampus were traced every 2 mm moving in the posterior–anterior direction. This resulted in 18–23 measured slices per person. The most anterior slice of the hippocampal head was determined retrospectively as the last slice on which the hippocampus was visible. Brain sections were inspected sequentially at 0.25 mm intervals until the hippocampus was no longer visible. The volume of that eight-interval stack was scaled proportionally. Cavalieri's principle was used to compute volume.

Total intracranial volume (TIV). Total intracranial volume was determined by tracing the margin of the inner table of the calvarium across sagittal 3D T1-weighted images (Supplementary Fig. 2) and summing up the volumes of sagittal slabs so obtained (Jack et al., 1989). Sections were traced every 6.6 mm, starting from the right side, totaling 17–22 measured slices per volunteer. The most lateral slice on which cerebral cortical gyri were first visible was traced first. The inferior-most limit to tracing was the region across the foramen magnum.

Total ventricular volume. Total ventricular volume was obtained as a sum of the volumes of two lateral, third and fourth ventricles (Supplementary Fig. 2). These were traced every 3 mm. Left and right lateral ventricles were measured simultaneously in the posterior–anterior direction, totaling 22–28 measured slices per participant. The slice in which the occipital horns of the lateral ventricles were visible first was traced first. The slice in which the frontal horns of the lateral ventricles were visible was traced last. The third ventricle was traced starting with the slice on which the anterior to the commissure of the superior colliculus was visible first and ending with the slice posterior to the optic chiasm. Measurements of the fourth ventricle were taken from every third slice in which this structure was visible (approximately 5–7 slices per subject). Measurement began with the slice in which the inferior vermis was visible and ended when the obex was seen. The cerebral aqueduct was included in this measurement.

Inter-tracer reliability for manually traced volumes was evaluated by comparing measurements of 10 randomly selected brains made by two tracers on two different occasions and separated by at least four weeks. The intra-class correlation coefficient or ICC (Shrout and Fleiss, 1979) were 0.93 for HC, 0.99 for TIV, and 0.99 for ventricles.

Automated measurements. Automated measurements of brain volumes were performed using FreeSurfer 3.0.5 (http://surfer.nmr.mgh.harvard.edu/). Briefly, this involved the removal of non-brain tissue using a hybrid watershed algorithm (Segonne et al., 2004), bias field correction, automated Talairach transformation, segmentation of subcortical white matter and gray matter (including hippocampus, ventricles) (Fischl et al., 2002; Fischl et al., 2004), intensity normalization, tessellation of the gray/white matter boundary, automated correction of topology defects, surface deformation to form the gray/white matter boundary and gray/cerebrospinal fluid boundary, and parcellation of cerebral cortex (including frontal cortex, parietal cortex, occipital cortex) (Desikan et al., 2006; Salat et al., 2004) based on gyral and sulcal information derived from manually traced brains. Morphometric evaluation of each hemisphere was conducted independently. In the present work, we report total cerebral, total gray and total white matter volumes involving the cerebral hemispheres (excluding brain stem and cerebellum; see below) as well as selected cortical structure gray matter volumes. All of these measures were corrected for eTIV before statistical analysis.

Estimated total intracranial volume (eTIV). The eTIV was calculated using a validated method described elsewhere (Buckner et al., 2004). Briefly, an Atlas Scaling Factor (ASF) was determined based on the transformation matrix of atlas normalization for each individual subject. The ASF was then used to scale the TIV of the standardized atlas brain to compute a given subject's TIV.

Head-size adjustment: All the volumetric measurements reported here showed significant gender differences before adjusting for head-size differences. The adjustment was performed on each volume of interest using the following analysis of covariance approach (Buckner et al., 2004; Mathalon et al., 1993):

$$Vol_{adj} = Vol_{raw} - b \times (TIV - \overline{TIV})$$

where b is the slope of the linear regression between the brain volume of interest and TIV . Note that this correction was not applied for cortical thickness measures.

Total cerebral volume (TCV). This was defined as the total volume of cerebral gray matter, cerebral white matter, and subcortical structures excluding the cerebellar hemispheres. Constituent sub-volumes were summed together *before* adjusting for head size differences.

Total ventricular volume. This was defined as the total volume of lateral ventricles, third ventricle and fourth ventricle. As ventricular measurements are positively skewed, we log-transformed the raw measurements before making adjustments for differences in head-size.

Hippocampal volume. The anatomical conventions employed by FreeSurfer for this measurement differ from those outlined for manual measurement in the current study. FreeSurfer estimates of hippocampal volume were systematically higher than for manual measurement. Adjustments for head-size differences were performed separately for

left, right and total hippocampal volumes. We reported these values for comparison purposes but did not use them in our analyses.

Cerebral cortex gray matter and white matter volume. FreeSurfer computes the volume of cortical gray matter using two methods — a model based surface processing pipeline and a voxel based volume pipeline. The latter is an intensity-based method similar to that used in voxel based morphometry packages like SPM. Here, we used the output of the surface pipeline, which modeled the cortical surface after detecting the gray-white boundary and then 'growing' the pial surface of gray matter. This yielded an estimate of the gray matter volume of cerebral cortical surface (excluding subcortical nuclei like the basal ganglia and thalamus) in addition to providing direct measures of cortical thickness at each vertex. Cerebral white matter volume was estimated by subtracting the volume of subcortical nuclei and ventricles from the contents of each cerebral hemisphere enclosed within the modeled gray matter mantle. These procedures comply with recommendations made in the FreeSurfer Wiki at http://surfer.nmr.mgh.harvard.edu/fswiki.

Parcellated cortical structure volumes. The surface parcellation procedure in FreeSurfer automatically assigns a neuroanatomical label to each gray matter voxel. This allows extraction of the gray matter volume for each cortical structure in a manner that has been validated against expert manual tracing (Desikan et al., 2006). In the current work, we selected a subset of FreeSurfer defined cortical regions based on prior structural and functional imaging data that related structure to cognitive functions of interest (see Greenwood, 2007; Raz, 2005; Reuter-Lorenz and Lustig, 2005 for recent reviews). These were inferior frontal, superior frontal, inferior parietal, superior parietal, lateral occipital, lingual cortex, pericalcarine cortex, and fusiform cortex (Fig. 1) Parcellated volumes and cortical thickness measures were corrected for eTIV.

Annualized percentage change (APC) values for the various brain volumes were estimated using the method proposed by Raz (Raz et al., 2003b):

$$\mathrm{APC} = \frac{Vol_b - Vol_a}{Vol_a \times (b-a)} \times 100$$

where b is the upper limit of the sample age range while a is the lower limit of the sample age range. Vol_a and Vol_b are the predicted brain volumes at age and respectively using the regression equation from the cross-sectional regression of brain volume with age. In the current report $a = 55$ years and $b = 86$ years.

Related data

In addition to the tests described above, each participant provided sociodemographic information (education, housing type), details concerning substance use (cigarette and alcohol consumption), dietary history, exercise and leisure activity, as well as medication and supplement intake. Weight, height and blood pressure were measured. Education was categorized into 5 classes: no formal education, 1–6 years, 7–9 years, 10–12 years and >12 years. These age bands represent points at which either scholastic ability or socio-economic factors resulted in a person having to leave school. The second band represents primary education. The third represents school leaving age for some of the older persons (a limitation of the education system at that time and locale). The fourth represents completion of secondary education whereas the fifth band indicates eligibility for college or higher technical education. Over the last 60 years, Singapore has transformed from a country when less than 1% had a college education to one where presently 25% are college educated accounting for the range of education in this cohort.

A person was termed hypertensive if he/she had a systolic blood pressure of ≥140 mm/Hg or a diastolic BP of ≥90 mm/Hg or was on treatment for hypertension, irrespective of the blood pressure measurement taken for that day. A diabetic was defined as someone with a fasting whole blood glucose level of ≥7.0 mmol/l or a person on treatment for diabetes mellitus.

Statistical analysis

Of the 349 respondents, 248 were deemed suitable for cross-sectional data analysis according to the inclusion criteria and imaging quality control measures previously outlined. Of the 101 participants that were excluded: Twenty (5.73%) either declined to undergo MR imaging or had images that were of insufficient quality, 4 (1.5%) showed pathological brain abnormalities on MR — we did not exclude individuals with small basal ganglia infarcts that were asymptomatic; 19 had significant health problems missed on initial screening; 17 (4.87%) underwent coronary artery bypass surgery (patients with

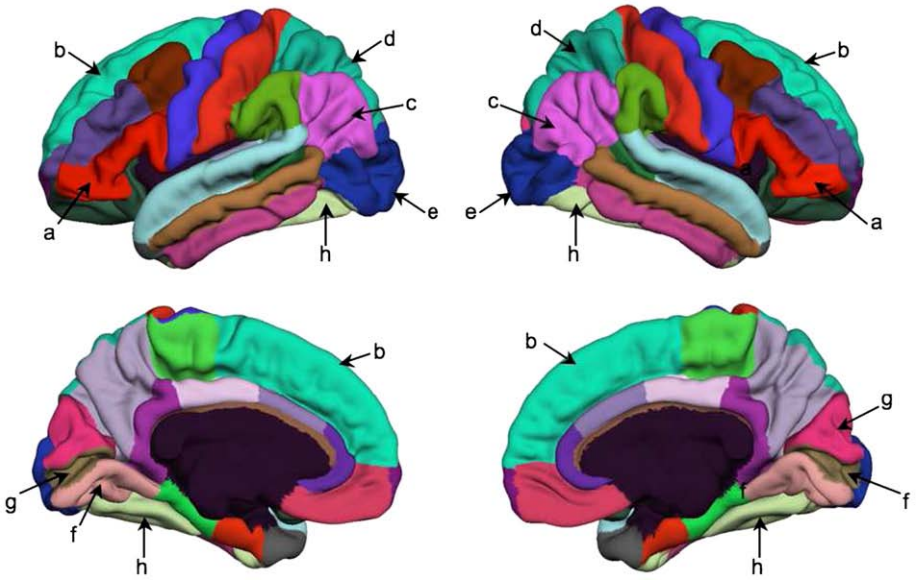

Fig. 1. Brain surface parcellated into regions by FreeSurfer from data obtained from 236 volunteers. (a) Inferior frontal cortex; (b) Superior frontal cortex; (c) Inferior parietal cortex; (d) Superior parietal cortex; (e) Lateral occipital cortex; (f) Lingual cortex; (g) Pericalcarine cortex; (h) Fusiform cortex.

stents were excluded outright) and 2 (0.57%) had obstructive sleep apnoea; 35 (10%) had a MMSE score <26; 6 (1.7%) had a Geriatric Depression Screening Scale (GDS) score >9; and 24 were not right handed (left-handed; $n=12$ (3.44%)), ambidexterous ($n=12$; (3.44%)).

Of the 248 eligible participants, 236 participants contributed complete brain imaging data as 12 participants had MR images that did not meet the stringent quality standards required for FreeSurfer analysis. This was a result of low contrast between gray and white matter in the occipital region. The overall strategy for analysis was to study the correlates of age with cognition and brain measures, followed by other variables of interest with cognition and brain measures and finally the association between brain measures and performance in 6 cognitive domains of interest. Partial correlations were used to analyze the associations between other variables of interest and cognition or brain measures after factoring out confounding covariates. The significance of these correlations was reported both prior to ($p<.05$) and after Bonferroni correction for multiple comparisons (adjusted threshold: $p<.008$). Multivariate linear regression was applied to study the independent effect of age on cognition after controlling for gender, education, BMI (body mass index = weight/(height)^2), height and homocysteine. We applied Steiger's Z^* statistic (Stieger, 1980) when determining whether slopes of cognitive decline (or volume decline) vs. age were significantly different across cognitive measures (or brain measures) (Raz et al., 1997; Salat et al., 2004). Folate, homocysteine and vitamin B12 values were log transformed prior to further analysis. Data analysis was performed using SPSS version 16.0 (SPSS Inc, Chicago IL).

Results

Characteristics of the study population

The cohort was matched for age and gender (men: mean = 65.9, SD = 6.9 years and women: mean = 65.6, SD = 6.1 years; women 52.8%; Table 1). 84% of participants had at least 10 years of education, substantially higher than that reported in a larger community-based longitudinal aging study conducted in the same city (Feng et al., 2006) but lower than that reported in most studies on Caucasian subjects. For comparison the *national average* in 1997 for resident non-students >25 years of age was 8.8 for men and 7.1 years for women (http://www.singstat.gov.sg/stats/charts/lit-edu.html). Men were generally better educated (mean = 11.4 years, SD = 3.1) than women (mean = 10.1 years, SD = 3.6).

57.3% of volunteers were hypertensive of which 72.5% were on treatment. 12.5% of volunteers had diabetes mellitus of which 94.5% were on treatment. 40.7% of all volunteers were not on any prescription medication. There were few smokers (3.2%). The mean BMI of this cohort was 23.4 (SD = 3.03). While low relative to Caucasian data, this figure is average in the East Asian context. For similar levels of BMI, East Asians have been found to be at higher risk for adverse cardiovascular outcomes (Deurenberg-Yap et al., 2000; Deurenberg and Deurenberg-Yap, 2003).

Table 1
Characteristics of the sample

n	248
Age, years	65.8 (6.53)
Women, %	131 (52.8)
Education, years	10.7 (3.46)
BMI, kg/m^2	23.4 (3.03)
Systolic BP, mm Hg	132 (16.1)
Diastolic BP, mm Hg	80.2 (9.23)
Hypertension (all), %	57.3
Fasting blood glucose, mmol/L	5.3 (1.0)
Diabetes, %	12.5
Total cholesterol, mmol/L	5.41 (0.89)
LDL-C, mmol/L	3.30 (0.78)
HDL-C, mmol/L	1.46 (0.36)
Homocysteine, μmol/L	13.7 (4.36)
Folate, nmol/L	25.9 (16.0)
Vitamin B-12, pmol/L	431 (221)
Ex-smoker	51 (20.6)
Current smoker	8 (3.2)
Do not consume alcohol	199 (80.2)
APOE-ε4 heterozygotes[a]	46 (18.5)
MMSE score	28.5 (1.16)
GDS score	1.56 (1.76)

Values other than for gender are means (SD) or n (%). Abbreviations: BMI, Body-Mass Index; LDL, Low Density Lipoprotein; HDL, High Density Lipoprotein; APOE-ε4, Apolipoprotein Epsilon-4 allele.
[a] There were no APOE-ε4homozygotes in this cohort; MMSE, Mini-Mental State Examination; GDS, Geriatric Depression Scale.

Table 2
Cognitive measures and their correlation with age

Cognitive domains	Neuropsychological Test	*N*	Mean	SD	r_{age}
Attention	Digit span forward	248	10.6	2.51	−0.21**
	Digit span backward	248	6.15	1.91	(−0.19**)
	Spatial span forward	248	7.25	1.89	
	Spatial span backward	248	6.31	2.12	
Speed of processing	Symbol digit modalities test (written)	248	42.5	10.3	−0.41*** (−0.42***)
	Symbol digit modalities test (oral)	248	49.4	10.6	
	Trail-making test A	248	45.1	19.3	
Verbal memory	RAVLT				−0.22**
	Sums of trials 1–5	248	45.6	9.01	(−0.20**)
	Immediate recall list A	247	9.77	2.88	
	Delayed recall list A	248	9.88	3.02	
	Recognition list A	246	13.4	2.02	
	Verbal paired associates				
	Sums of trials 1–4	236	10.6	7.41	
	Delayed recall	236	3.74	2.56	
	Recognition	246	13.39	2.02	
Visuospatial memory	Visual reproduction				−0.22**
	Immediate recall	248	68.4	14.7	(−0.19**)
	Delayed recall	248	44.3	18.2	
	Visual paired associates				
	Sums of trials 1–4	246	16.59	5.89	
	Delayed recall	246	4.84	2.25	
Executive function	Categorical fluency	248	42.82	8.64	−0.30***
	Design fluency	248	21.58	7.62	(−0.27***)
	Trail-making test B	230	119	97.6	
Language	Object naming	247	71.1	7.19	−0.22**
	Action naming	247	40.6	5.85	(−0.18**)

Figures in parenthesis refer to correlation between age and cognitive performance after correcting for gender and education.
* $p<.05$.
** $p<.01$.
*** $p<.001$.

Effect of age on cognitive performance

Performance in all six cognitive domains declined with age (Table 2) and this effect remained significant after adjusting for the effects of gender and education. The strongest correlation was seen between age and speed of processing ($r=-0.41$, $p<.001$), followed by executive function ($r=-0.30$, $p<.001$), visuospatial memory ($r=-0.22$, $p=.003$), language ($r=-0.22$, $p=.003$), attention ($r=-0.21$, $p=.002$) and verbal memory ($r=-0.22$, $p<.002$). The correlation between speed of processing and age was significantly higher than for other cognitive domains and age (Steiger's Z^* statistic = 2.78, $p<.05$).

Effects of other variables on cognitive performance

Gender and education accounted for significant variance in cognitive performance over and above age (Table 3). Men showed

Table 3
Effect of other variables on cognitive performance

Variable	Attention	Speed of processing	Verbal memory	Visuospatial memory	Executive function	Language
Gender: women[a]	−0.20**	−0.18**	0.25***	–	–	−0.20**
Education[b]	0.25***	0.55***	0.29***	0.33***	0.43***	0.47***
BMI[c], kg/m^2	(−0.14*)	−0.20**	(−0.18**)	(−0.16*)	–	(−0.14*)
Systolic BP[c], mm Hg	–	–	–	–	–	–
Diastolic BP[c], mm Hg	–	–	–	–	–	–
Fasting glucose[c] (mmol/L)	–	–	–	–	–	–
Total cholesterol[c] (mmol/L)	–	(0.15*)	–	–	–	–
Homocysteine[c] (μmol/L)	–	−0.20**	–	(−0.13*)	–	(−0.14*)
Folate[c] (nmol/L)	–	(0.13*)	–	(0.13*)	(0.14*)	(0.13*)
Vitamin B–12[c] (ρmol/L)	–	–	–	–	–	0.17**
Height[c]	–	–	–	0.16**	(0.13*)	(0.12*)
At least one e4 allele of APOE[c]	–	–	–	–	–	–

*p<.05; **p<.01; ***p<.001; If Bonferroni correction was used to account for multiple comparisons across the 6 cognitive variables, a corrected threshold of p<.008 was applied; correlations that did not meet this threshold appear parentheses.
[a] Gender was adjusted for age.
[b] Education was adjusted for age and gender.
[c] Other variables were adjusted for age, gender and education.

superior performance in 3 out of 6 cognitive domains. They scored higher on attention (r = −0.20, p = .001), speed of processing (r = −0.18, p = .006) and language (r = −0.20, p = .002), while women scored higher on verbal memory (r = 0.25, p<.001). These gender effects on attention (r = −0.16, p = .015) and verbal memory (r = 0.31, p<.001) were significant even after adjusting for the effects of age and education.

BMI continued to have a small but significant effect on speed of processing even after correcting for age, gender, education and multiple comparisons. In accordance with prior data from Caucasian populations (Schulz, 2007) as well as a prior study from the same city (Feng et al., 2006), higher homocysteine levels were negatively correlated with cognitive performance. Height, a proxy for early life brain development (Abbott et al., 1998; Beeri et al., 2005) was positively correlated with visuospatial memory. APOE ε4 status, systolic blood pressure and fasting blood glucose did not independently correlate with cognitive scores in this analysis. However, it should be noted that the ranges of blood pressure and glucose were restricted in this relatively healthy population.

Multivariate linear regression showed comparable findings for the effects of age on cognition after controlling for confounders — gender, education, BMI, height and homocysteine (Supplementary Table 1).

Comparison of manual and automated volumetric measurements

Automated measurements of TIV (r = 0.87; p<.001), total brain volume (r = 0.98; p<.001) and ventricles (r = 0.98; p<.001) were very highly correlated with manual measurements (Table 4). The correlation between manual and automated measures of the hippocampus was lower (r = 0.82; p<.001) as expected given the small size of this structure and the different landmarks used for segmenting this structure. As a result, further analyses utilized only manually measured hippocampal volumes.

Table 4
Comparison of manual and automatic volumetric measurements

Variables	Unadjusted		
	Manual	Automated	r
Total intracranial volume	1462.7 (130.6)	1399.1 (139.6)	0.87**
Total brain volume[a]	1009.4 (135.6)	1175.5 (137.2)	0.98**
Hippocampus	6.56 (0.72)	7.60 (0.83)	0.82**
Left hippocampus	3.22 (0.37)	3.66 (0.41)	0.79**
Right hippocampus	3.34 (0.37)	3.94 (0.44)	0.79**
Ventricular volume[b]	1.33 (0.18)	1.40 (0.17)	0.98**

Volumes are mean values (SD) in cm^3.
[a] TBV, n = 18 (includes cerebellum but excludes ventricles); for other measures n = 236.
[b] Correlations involving ventricular volumes were computed using log-transformed measures.
** all correlations were significant at p<.001.

Effects of age on brain measures

Men had larger heads than women as reflected by higher intracranial volume (Mean: men 1548 cm^3 vs. women 1386 cm^3; difference 11%; p<.001) but the effect of gender across *all* brain measures was negated after correcting for TIV/eTIV. This was in keeping with recent reports using higher quality brain imaging and measurement techniques (Buckner et al., 2004; Scahill et al., 2003).

After correcting for head size, which negated the influence of gender and height on these measures, total cerebral volume and total hippocampal volume showed significant age-related decline (Fig. 2). The correlation between age and total cerebral volume (r = −0.46; p<.001) was higher than the correlation between age and hippocampal volume (−0.37; p<.001). This might be expected from the greater variability arising from measuring a small complex structure like the hippocampus. Both total cerebral and total hippocampal volumes declined at approximately 0.45%/year, with wider 95% confidence intervals for the latter. Ventricles enlarged at a rate of around 4.9%/yr (Table 5).

Cortical surface gray matter volume declined at an estimated 0.33%/yr; 95% CI (−0.40 to −0.14%) and cerebral white matter volume contracted at a comparable rate of 0.41%/yr; 95% CI (−.60 to −0.25%); Table 6, Fig. 2. We found comparable regional rates of decline of gray matter volume across several cortical ROI in the frontal, parietal and occipital lobes (Table 6; Fig. 3). Apart from the lingual gyri, no other brain region showed a comparably robust rate of decline with age relative to total cerebral volume.

Effects of other variables on brain measurements

After correcting for head size, only plasma homocysteine showed any correlation with brain measures. Plasma homocysteine showed a negative correlation with white matter volume (r = −0.25, p<.001) and a positive correlation with ventricular volumes (r = 0.19, p<.005). There were no significant correlations between BMI, blood pressure, fasting blood glucose or total cholesterol and manually obtained brain measures. After accounting for age, only the effect of homocysteine on cerebral white matter volume (r = −0.18, p<.01) remained significant. In contrast to its strong effects on cognitive performance, education was not correlated with any brain measure, excepting a modest correlation with cortical thickness in the left inferior frontal region.

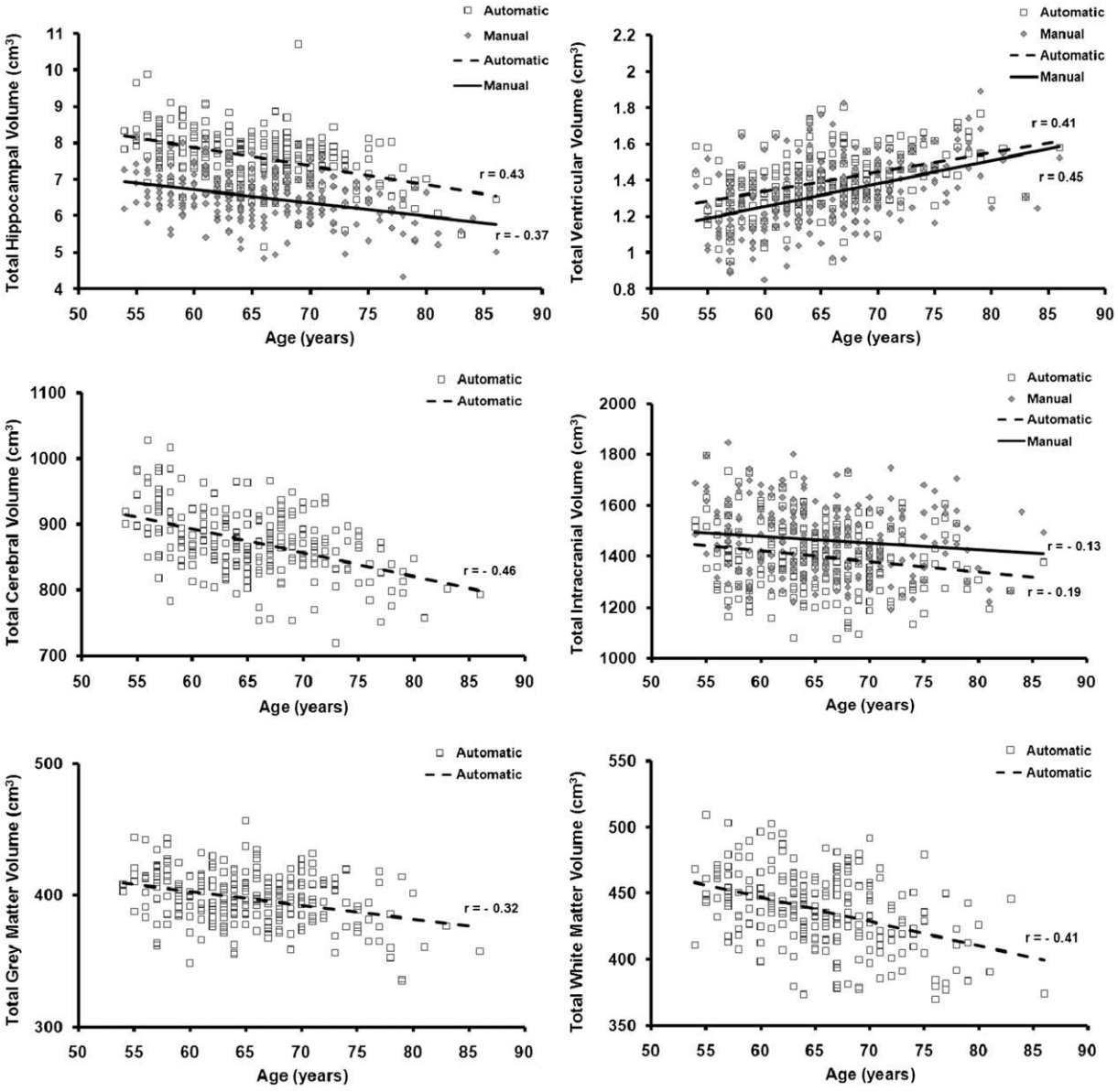

Fig. 2. Scatter plots depicting the effect of age on brain measures using automated ($n=236$) and manual ($n=248$) measurements. Ventricular volumes were log-transformed.

Correlations between brain measurements and cognitive performance

As older participants in this cohort had smaller heads (represented by TIV or eTIV; decline in TIV of 0.23%/yr) and since TIV or eTIV were used to normalize brain measurements, it was important to evaluate how this finding relates to cognitive performance. After accounting for age, we found no deleterious effects of smaller head size on any of the cognitive domains evaluated.

There were positive correlations between total cerebral volume and speed of processing ($r=0.28$, $p<.001$), visuospatial memory ($r=0.21$, $p<.001$), executive function ($r=0.19$, $p<.01$) and attention ($r=0.17$, $p<.01$; Table 7). Total ventricular volume correlated negatively with speed of processing ($r=-0.24$, $p<.001$), executive function ($r=-0.22$, $p<.001$) verbal memory ($r=-0.14$, $p<.05$) and visuospatial memory ($r=-0.14$, $p<.05$). The latter two correlations did not survive correction for multiple comparisons. These correlations were identical for both manual and automated measurements of total cerebral volume. Manually measured left hippocampal volumes showed weak positive correlations with visuospatial memory and executive function that did not survive correction for multiple comparisons and which were not replicated in the corresponding automated measures.

Within specific cortical regions of interest, speed of processing showed significant positive correlation with gray matter volume in bilateral inferior frontal (R: $r=0.24$, L: $r=0.18$, both $p<.01$; Fig. 4) and

Table 5
MRI imaging volume data: correlations between age and brain measures

ROI	Volume (cm^3) adjusted	r_{age}	Annual percentage change (95% CI)
Total cerebral volume	873.54 (50.58)	−0.46**	−0.40 (−0.57 to −0.27)
Hippocampus	6.52 (0.65)	−0.37**	−0.54 (−0.87 to −0.30)
Right hippocampus	3.32 (0.33)	−0.36**	−0.51 (−0.86 to −0.28)
Left hippocampus	3.20 (0.33)	−0.36**	−0.53 (−0.89 to −0.29)
Ventricular volume[a]	1.32 (0.18)	0.45**	4.85 (2.87–6.73)

Volumes were adjusted for total intracranial volume (TIV or eTIV as appropriate).
[a] Ventricular volumes were log-transformed prior to computing correlation.
** all correlations were significant at $p<.001$.

Table 6
Correlations between age and additional automatically determined brain measures

ROI	Brodmann area	Adjusted volume (cm^3)	r_{age}	Annual percentage change (95% CI)
Cerebral grey matter				
Right	–	199.77 (10.6)	−0.32**	−0.26 (−0.41 to −0.14)
Left		197.52 (10.1)	−0.33**	−0.26 (−0.40 to −0.14)
Cerebral white matter				
Right	–	239.18 (14.3)	−0.41**	−0.40 (−0.60 to −0.25)
Left		239.34 (14.2)	−0.40**	−0.40 (−0.60 to −0.25)
Inferior frontal gyrus				
Right	44,45,47	8.81 (1.1)	−0.17*	−0.33 (−0.80 to −0.05)
Left		8.67 (1.1)	–	–
Superior frontal gyrus				
Right	8, 9	18.07 (1.7)	−0.17*	−0.26 (−0.54 to −0.04)
Left		19.41 (1.8)	−0.22**	−0.30 (−0.46 to −0.10)
Inferior parietal cortex				
Right	19,39	11.89 (1.3)	−0.16*	−0.21 (−0.66 to −0.04)
Left		10.03 (1.2)	−0.17**	−0.32 (−0.79 to −0.06)
Superior parietal cortex				
Right	7	10.76 (1.2)	−0.17*	−0.30 (−0.71 to −0.06)
Left		10.79 (1.3)	−0.17**	−0.33 (−0.82 to −0.07)
Lateral occipital cortex				
Right	17,18,19	10.53 (1.5)	−0.21**	−0.46 (−1.09 to −0.14)
Left		10.58 (1.4)	–	–
Lingual				
Right	17,18	5.75 (0.8)	−0.33**	−0.69 (−1.34 to −0.32)
Left		5.13 (0.8)	−0.21**	−0.53 (−1.36 to −0.13)
Pericalcarine cortex				
Right	17	2.10 (0.3)	−0.15*	−0.38 (−1.18 to −0.03)
Left		1.66 (0.3)	–	–
Fusiform gyrus				
Right	37	6.91 (1.1)	–	–
Left		7.05 (1.2)	−0.15*	−0.39 (−1.2 to −0.04)

*$p<.05$; **$p<0.01$.

Table 7
Correlations between MRI brain measures and cognitive performance

Variable	Attention	Speed of processing	Verbal memory	Visuospatial memory	Executive function	Language
Total cerebral volume	0.17**	0.28***	–	0.21***	0.19**	–
Hippocampus	–	–	–	–	(0.14*)	–
Right hippocampus	–	–	–	–	–	–
Left hippocampus	–	–	–	(0.13*)	(0.16*)	–
Ventricular volume[a]	–	−0.24***	(−0.14*)	(−0.14*)	−0.22***	–

*$p<.05$; **$p<.01$; ***$p<.001$. If Bonferroni correction was used to account for multiple comparisons across the 6 cognitive variables a corrected threshold of $p<.008$ was applied; correlations that did not meet this threshold appear parentheses.
[a] Ventricular volumes were log-transformed prior to computing correlation.

superior parietal regions (R: $r=0.18$, $p<.01$) as well as the lingual gyrus (R: $r=0.21$. $p<.001$, Table 8). Notably, in the automated parcellation scheme used here, the lingual gyrus is adjacent to the inferior lip of the pericalcarine cortex that was referred to as 'pericalcarine cortex' (Raz et al., 2005) and 'primary visual cortex' (Salat et al., 2004) in prior studies. Left superior frontal gyrus cortical volume showed significant positive correlations with attention, speed of processing and visuospatial memory.

When the effects of age were controlled for, most of the significant correlations disappeared except for those relating speed of processing to both inferior frontal gyri (L: $r=0.17$, R: $r=0.19$, both $p<.01$) as well as attention in relation to the right lingual gyrus ($r=0.15$, $p<.05$), indicating that age accounted for most of the observed variance.

Discussion

The present cross-sectional study is the first sizable combined MRI imaging, neuropsychological and health variable study performed on a cohort of healthy aged volunteers arising from a single, East Asian ethnic group. The study cohort is unique in that most participants were born and grew up in a developing country but aged in a developed one.

We found speed of processing to be the most age-affected cognitive domain. It was associated with commensurate decline in total cerebral hemisphere volume. White matter volume loss was at least as prominent as gray matter decline. Regionally, there was relatively greater volume loss in the lateral prefrontal cortex bilaterally, around

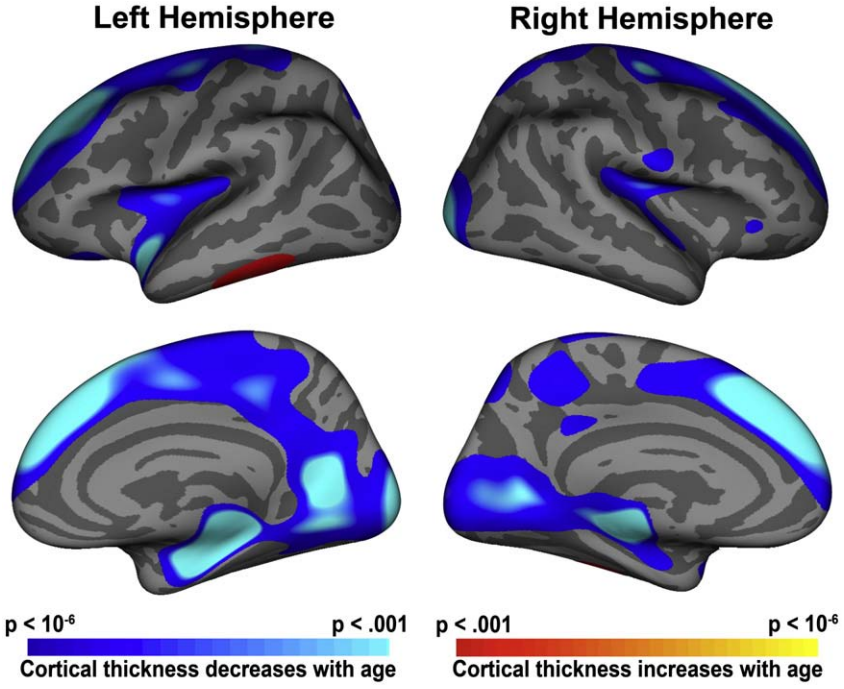

Fig. 3. Surface maps of age-related cortical thinning (blue) obtained after controlling for eTIV. On the inflated brain, dark gray regions represent gyri and lighter areas represent sulci.

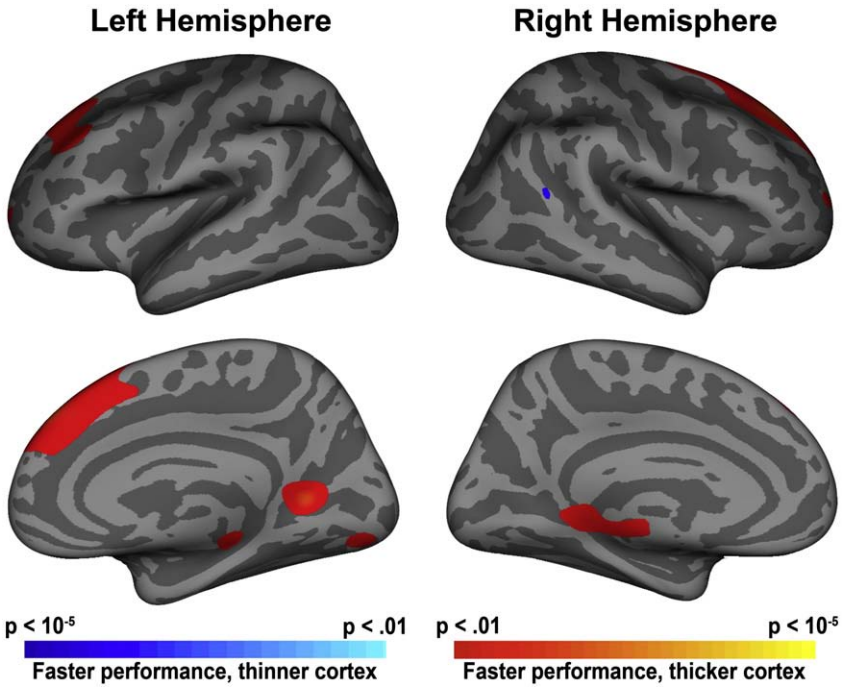

Fig. 4. Surface maps showing cortical areas in which there was significant correlation between cortical thickness and speed-of-processing scores (after controlling for eTIV).On the inflated brain, dark gray regions represent gyri and lighter areas represent sulci.

the primary visual cortex as well as bilateral superior parietal cortices. Contrary to popular expectation, despite differences in diet, lifestyle, body structure and a lower frequency of APOE e4 carriers in our East Asian cohort, the pattern of change in cognition and brain measures was broadly comparable to similar studies conducted in Caucasian populations and speaks to the generalizability of processes involved in age-related decline in cognition and brain volume.

Table 8
Correlations between regional brain volumes and cognitive performance

Variable	Attention	Speed of processing	Verbal memory	Visuospatial memory	Executive function	Language
Cerebral grey matter						
Left	–	0.17**	–	0.18**	(0.16*)	–
Right	–	(0.14*)	–	(0.16*)	(0.13*)	–
Cerebral white matter						
Left	(0.17*)	0.27**	0.23**	0.19**	0.29**	(0.15*)
Right	(0.15*)	0.26**	0.22**	0.20**	0.28**	(0.15*)
Inferior frontal gyrus						
Left	–	0.18**	–	–	–	–
Right	(0.15*)	0.24**	–	–	(0.14*)	–
Superior frontal gyrus						
Left	(0.15*)	(0.15*)	–	(0.14*)	–	–
Right	–	–	–	–	–	–
Superior parietal cortex						
Left	–	(0.13*)	(0.15*)	–	–	–
Right	–	0.18**	–	(0.14*)	(0.14*)	–
Lingual						
Left	–	(0.15*)	–	–	–	(0.13*)
Right	0.20**	0.21**	–	0.18**	(0.14*)	–
Fusiform gyrus						
Left	–	–	–	(0.13*)	–	–
Right	–	–	–	–	–	–

*$p<.05$; **$p<.01$. There were no significant correlations between cognition and brain measures in the inferior parietal cortex, lateral occipital cortex and pericalcarine cortex. If Bonferroni correction was used to account for multiple comparisons across the 6 cognitive variables a corrected threshold of $p<.008$ was applied; correlations that did not meet this threshold appear parentheses.

Decline in cognition with age and effects of other variables

We found that age affected speed of processing more severely than other cognitive domains. Education exerts considerable influence on cognitive performance (Staff et al., 2004) and, in this cohort, it had a large effect on speed of processing and executive function, contributing 30% and 18.5% of the variance in these cognitive domains respectively. The elderly in the present study had 3–5 years less formal education compared to volunteers in prior imaging studies (Fotenos et al., 2005; Raz et al., 2005). Despite this difference, most of the structural imaging findings we observed were quite similar to those reported in Caucasian populations.

Consistent with several cross-sectional (Duthie et al., 2002; Elias et al., 2005; Feng et al., 2006) and prospective (Kado et al., 2005; Nurk et al., 2005) studies on aged individuals, we found elevated homocysteine levels to be associated with poorer cognitive performance, serving to generalize these findings to a population with different dietary habits. More specifically, elevated levels of homocysteine were linked to psychomotor slowing (Prins et al., 2002; Schafer et al., 2005) and poorer episodic visual memory (Elias et al., 2005). Plasma concentrations of folate were weakly associated with speed of processing, executive functions and episodic visual memory (de Lau et al., 2007; Feng et al., 2006; Ramos et al., 2005). While homocysteine and folate levels were correlated ($r=0.4$, $p<0.01$), they appear to exert dissociable effects on the brain as evidenced by their differential effects on brain measures.

Age-related brain atrophy: independent of education or cohort effects on head size

The negative correlation between intracranial volume and age observed here has not been reported in studies conducted in developed countries, when only elderly volunteers were analyzed (Edland et al., 2002; Jenkins et al., 2000; Lemaitre et al., 2005; Raz et al., 2005) possibly reflecting the poorer early-life socio-economic conditions and nutrition in the current cohort.

Intracranial size has been suggested as a surrogate marker of 'cognitive reserve' (MacLullich et al., 2002; Schofield et al., 1997), but several studies have found no correlation between head size and risk of dementia (Edland et al., 2002; Jenkins et al., 2000). Here, we found no deleterious association between intracranial size and cognitive scores apart from attention. Although men had larger heads than women, the effects of gender on brain measures were not significant after correcting for head size, as in previous studies (Buckner et al., 2004; Lemaitre et al., 2005).

Age-related changes in brain measures

Total brain volume is the most extensively reported measure in brain aging research and is associated with an annual percent change (APC) of 0.18–0.88%/yr with an average around 0.5%/yr in the age group we tested (Jack et al., 2005; Preboske et al., 2006; Raz et al., 2007). Another well-studied metric is hippocampal volume; APC 0.3–1.5%/yr depending on age (Fox and Schott, 2004; Jack et al., 2005). Our cross-sectional estimates concerning both measures (total cerebral volume APC 0.4%/yr; hippocampal APC 0.5%/yr) are at the low end relative to studies that evaluated or analyzed only elderly subjects (Fotenos et al., 2005; Raz et al., 2005) but are higher than reports that evaluated volume change from young adulthood to senescence (Jernigan and Gamst, 2005). In addition to rate of decline, the variance of brain measures and whether they increase in the oldest old (Scahill et al., 2003) or not (Fotenos et al., 2005) is important to consider. Our relatively healthy cohort did not show increased variance of brain measures with age (see scatter plots in Fig. 2).

White matter volume declined at an equivalent rate as gray matter volume in the present cohort. This is in keeping with other newer studies involving elderly volunteers (Fotenos et al., 2005; Ikram et al., 2008) as well as some studies evaluating volumes across a large age span (Guttmann et al., 1998). Since white matter volume peaks as late as the fourth decade of life (Bartzokis et al., 2003), studies that evaluate age effects on white matter volume across the life span may yield smaller estimates of white matter decline or show no significant changes (Pfefferbaum et al., 1994). We did not find more precipitous decline with increasing age as suggested by some (Guttmann et al., 1998) although this might be a result of having few very old (>85 years) participants.

Age-related change in white matter volume in both hemispheres (Table 8) roughly paralleled the corresponding declines in domain specific performance (Table 2) in keeping with the notion that white matter changes play an important role in age-related cognitive decline (Bucur et al., 2008; Walhovd and Fjell, 2007).

Like others, we found regional differences in age-related brain atrophy (DeCarli et al., 2005; Jernigan et al., 2001; Lemaitre et al., 2005; Raz et al., 1997, 2005; Resnick et al., 2003; Salat et al., 2004). There is uniform agreement that age-related decline of frontal lobe volume occurs primarily in the lateral prefrontal (Raz et al., 2005; Salat et al., 2004) and/or orbito-frontal cortex (Lemaitre et al., 2005; Raz, 2005; Resnick et al., 2003). The present study concurred, and additionally identified significant age-related decline in lateral prefrontal cortex volume.

There is less agreement concerning regional atrophy elsewhere in healthy elderly volunteers. After the frontal lobe, some studies have reported lateral temporal atrophy (DeCarli et al., 2005; Jernigan et al., 2001) whereas others have emphasized shrinkage of the parietal lobes (Lemaitre et al., 2005; Resnick et al., 2003). There is strong disagreement regarding the occipital lobe around the primary visual cortex where cortical thinning has been reported as being prominent (Lemaitre et al., 2005; Salat et al., 2004) or insignificant (Raz et al., 1997, 2005). The cortical mantle in this region is very thin and it is possible that older MR image data may not contain sufficient resolution to make the distinctions that newer systems can (the important point is that the point spread function of the imaging data is the appropriate measure of revealed anatomical detail and not 'resolution' as measured by the density of the imaging matrix).

Using a similar methodology to Salat, we reproduced the finding that there is age-related thinning around the primary visual cortex and a striking absence of significant changes in the lateral temporal neocortex (Salat et al., 2004). This finding serves to remind that before evaluating the significance of regional changes in brain volume with age, the critical reader should take into account the lack of common analysis methodology across studies (but see (Kennedy et al., 2008)) as well as the heterochronicity of age-related regional changes in cortical thickness (Salat et al., 2004; Sowell et al., 2003). When considering the findings of the present study, it should be kept in mind that the age range used was restricted to subjects from 55–85 years and unlike life-span studies on aging, will necessarily show smaller correlations between age and structural brain measures.

Effects of other variables on brain measures

While there was a clear effect of education on cognitive performance, particularly in speed of processing, education did not influence age-related decline of total cerebral volume (adjusted for eTIV). Education explained some of the variance associated with cortical thickness in the left inferior frontal region, a region that also showed correlations with speed of processing. This finding contrasts with reports suggesting that non-demented elderly individuals with better education have a higher 'brain reserve' and may remain cognitively intact despite harboring greater brain atrophy (Coffey et al., 1999; Fotenos et al., 2008). The dissociation between overall brain volume and the cognitive benefit of education suggests that the latter may primarily operate at the level of synaptic function, or improved neuronal connectivity rather than increasing neural bulk in a regionally specific fashion as suggested by studies involving specific cognitive abilities like navigation, juggling or musical talent (Draganski and May, 2008).

Of the vascular risk factors, higher blood pressure (Goldstein et al., 2002; Heijer et al., 2003; Wiseman et al., 2004), elevated homocysteine (den Heijer et al., 2003; Sachdev et al., 2004), BMI (Gustafson et al., 2004; Ward et al., 2005) and diabetes (van Harten et al., 2006) have been associated with greater brain atrophy. However, the brain measurement techniques in these patient based studies are crude compared to those applied to the evaluation of healthy cognitive aging, MCI or AD.

Here, we found that although elevated homocysteine was associated with cerebral white matter atrophy and ventricular volume, this effect was not pronounced enough to consistently affect total cerebral volume. Prior studies have shown that whereas there is strong agreement that elevated homocysteine negatively affects cognition there is less agreement as to whether this is mediated through brain atrophy (den Heijer et al., 2003) or white matter hyperintensities (Sachdev et al., 2004). Although elevated BMI had a negative effect on cognition, we did not find correlations between BMI and brain volumes. There were no significant correlations between blood pressure or blood sugar on brain volumes. However, this could be a result of range restriction of these values in this healthy cohort.

Total cerebral measures may suffice in assessing cognition–brain structure relationships in healthy subjects

We found that adjusted total cerebral volume was the brain measure that showed the highest correlation with variables that affected cognition as well as with age-related change in cognitive performance. Correlations of this metric with speed of processing, executive function, visuospatial memory and attention were always positive, in keeping with the 'bigger is better' relationship between

whole brain volume and cognition (Posthuma et al., 2002; Staff et al., 2006; Walhovd et al., 2005).

In contrast, although hippocampal volume parallels memory decline in Alzheimer's disease (Jack et al., 1998), this correlation does not extend to healthy, non-demented volunteers evaluated using memory measures commonplace in clinical practice (Rodrigue and Raz, 2004; Van Petten, 2004). Only in the context of specialized testing, such as when long-term memory was tested 11 weeks after encoding has hippocampal volume in normal elderly been correlated with memory performance (Walhovd et al., 2004). It should be noted that the anatomical structures supporting such memories in healthy individuals could also include neocortical regions (Walhovd et al., 2006).

The advent of automated cortical segmentation that has been validated across scanners provides a potentially important advance in enabling the correlation of cognition and regional cortical thickness (Dickerson et al., 2008). However, the results of the present study suggest that while regional differences in correlations between different cognitive domains exist, the effects are small and may not be larger than the effects found using whole brain, total gray or white matter volumes. This said, it remains possible that as in the case of the hippocampus and memory, or executive function and the frontal lobes (Van Petten et al., 2004) the dissociation between more specific structural–cognition relationships when comparing normal subjects and patients with lesions could reflect the insensitivity of neuropsychological tests designed for clinical use.

Summary

The broad agreement between age-related changes in cognition and brain measures reported here compared to studies based on Caucasian populations argues for the presence of common factors that modulate brain aging across ethnic groups that potentially differ in culture, diet and lifestyle. Total cerebral measures appear to provide adequate brain–cognition correlations with performance on clinical neuropsychological tests in healthy elderly. However, to evaluate the structural neural correlates of variables that modulate cognition in this population, more sensitive neuropsychological tests or measures of structural integrity like diffusion tensor imaging may be helpful.

Disclosure

The authors have no conflict of interests to disclose. All authors have reviewed the contents of the manuscript being submitted, approve of its contents and validate the accuracy of the data.

Acknowledgments

Arne Littmann provided proprietary homogeneity correction and gradient distortion correction techniques. Jenni Pacheco provided on-site training for the use of FreeSurfer. Cliff Jack provided valuable advice on manual morphometry and the quality control aspects of this study. This work was supported by the Biomedical Research Council, Singapore: BMRC 04/1/36/372 and A*STAR: SRP R-913-200-004-304.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2009.01.036.

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