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Longitudinal brain structure and cognitive changes over 8 years in an East Asian cohort

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ABSTRACT

Although East Asia harbors the largest number of aging adults in the world, there is currently little data clarifying the longitudinal brain-cognition relationships in this group. Here, we report structural MRI and neuropsychological findings from *relatively healthy* Chinese older adults of the Singapore-Longitudinal Aging Brain Study cohort over 8 years of follow up (n=111, mean age=67.1 years, range=56.1–83.1 years at baseline). Aging-related change in structural volume was observed, with total cerebral atrophy at −0.56%/year, hippocampal atrophy at −0.94%/year and ventricular expansion at 3.56%/year. Only speed of processing showed an aging-related decline, while other cognitive domains were relatively maintained. Faster decline in global cognition was associated with total cerebral, hippocampal and gray matter volume losses over time. Faster total cerebral atrophy and white matter atrophy (frontal and parietal regions) was associated with faster decline in verbal memory. Hippocampal atrophy and ventricular expansion were both associated with greater decline in verbal memory and executive function. Our findings provide a benchmark for research on brain structural and cognitive changes with aging in East Asians.

1. Introduction

Better preservation of cognition with aging is an important goal with the burgeoning growth in older citizens in developed nations. While cross-sectional and longitudinal studies over the past few decades have provided insights into the neural correlates of age related cognitive changes, the bulk of published research on aging humans comes from the West (Stanziano et al., 2010). As factors influencing health and aging exhibit sociocultural and geographical differences (Cassarino and Setti, 2015), we sought to examine brain-cognition linkages in East Asians as well as to establish aspirational norms of brain and cognitive change for healthy aging in this less well characterized population.

Different brain areas exhibit heterogeneous trajectories in aging (Fjell et al., 2013). Age-related brain atrophy in frontal regions (Resnick et al., 2003; Chee et al., 2011; Fjell et al., 2009; Raz and Rodrigue, 2006) and the hippocampus (Fraser et al., 2015; Jack et al., 1998; Raz et al., 2004) have been clearly documented, while other areas such as parietal and occipital cortices appear less affected by aging (Raz et al., 2005; Good et al., 2001). In addition, gray and white matter volume display different age effects, with the former showing linear decline starting from middle adulthood, and the latter exhibiting more inconsistent patterns with age (Giorgio et al., 2010; Pfefferbaum et al., 1994; Walhovd et al., 2005).

Heterogeneous patterns have been similarly established for different cognitive domains (Goh et al., 2012; Hultsch et al., 2000; Wilson et al., 2002). While some domains of memory, e.g. vocabulary and general knowledge, appear preserved up to at least 60 years of age, speed of processing has been consistently found to decrease with age (Kennedy and Raz, 2009; Salthouse, 2010). The co-evolution of cognitive and volumetric brain changes with age prompt questions regarding their association. Some studies have demonstrated tentative links between regional changes in brain structure and specific cognitive domains, such as with medial temporal lobe volume and memory (Chen et al., 2010; Yonelinas et al., 2007; Ystad et al., 2009), or with gray and white matter volume and executive function (Chee et al., 2009; Raz et al., 2008; Brickman et al., 2006). However, discrepancies exist (Van Petten et al., 2004), and a major limitation in aging research remains to be the reliance on cross-sectional data.

While cross-sectional designs can generate data more quickly, unlike longitudinal studies they do not allow the separation of group and individual effects of aging (Salthouse, 2010; Hofer and Sliwinski, 2001). The few longitudinal studies investigating the relationship between changes in brain structure and multiple cognitive domains have yielded varied

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results. Some studies have found an association of total cerebral atrophy with declines in memory and speed of processing (Charlton et al., 2010; Cohen et al., 2001; Schmidt et al., 2005), while others have linked hippocampal atrophy with memory decline (Kramer et al., 2007; Mungas et al., 2005). Different results might be attributed to relatively small sample size and short follow-up duration in some studies.

Existing longitudinal cognitive aging studies in Asia have mostly examined cognition using omnibus measures, which only provide an overarching snapshot of cognitive function (Sachdev et al., 2013). To date, none have examined the links between longitudinal brain and cognitive changes in specific cognitive domains. Here, we provide an East Asian perspective on longitudinal brain and cognitive aging and report data collected over 8 years from 111 relatively healthy older adults from the Singapore-Longitudinal Aging Brain Study. Singapore is an economically successful nation nestled within a massive developing region. Our present cohort of elders represents a healthy and relatively well-educated subgroup of their birth cohort. As such, the present data is intended to represent an aspirational level of aging-related cognitive and brain structural changes for East Asians.

2. Methods

2.1. Participants

Participants were relatively healthy, community-dwelling, ethnic Chinese older adults in the Singapore-Longitudinal Aging Brain Study (SLABS) – a longitudinal study that seeks to characterize aging-related brain and cognitive changes in Singaporean-Chinese older adults. Participants were recruited from newspaper advertisements, healthy aging clubs, and by word of mouth (Chee et al., 2009). At the study outset in 2005, participants were aged 55 years and older. Participants returned for follow-up visits every 18–24 months. Due to a change in the MRI system after Phase 1, Phase 2 was used as the baseline phase in all the analyses in order to preserve standardization of the imaging data. Data from Phase 2 (2007–2009; n=289), 3 (2009–2010; n=219), 4 (2011–2012; n=150), and 5 (2013–2014; n=111) are reported here.

For the present analyses, participants were excluded if they had any of the following in *any* of the phases: (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-item modified Geriatric Depression Screening Scale (GDS) (Sheikh and Yesavage, 1986) score > 5; or (9) a history of illicit substance use. Although the MMSE is not a diagnostic test for dementia, it is useful for assessing the level of mental impairment in follow-up studies (Raz et al., 2005; Raz et al., 2010). In order to track brain and cognitive health of our participants, a neurologist examined the brain scans for each participant at each phase and participants were required to divulge all relevant medical information with researchers at each follow-up.

In the present analyses, we only included participants who had at least two phases of both imaging and neuropsychological data. Brain volume data from five participants were of low quality for at least one time point because of technical errors. As such, the analyses described here were based on a sample of 111 older adults, 24 with two time points, 25 with three time points, and 62 with four time points.

This study protocol was approved by the National University of Singapore Institutional Review Board. Participants provided written informed consent prior to evaluation.

2.2. Neuropsychological assessment

Cognitive function was assessed between 9 am and 12 pm using a battery of 10 standard tests evaluating five cognitive domains: **Speed of processing**—processing efficiency was measured by the Trial-Making Test-T A (Reitan and Wolfson, 1985), Symbol Search Task in the Wechsler Memory Scale – Third Edition (Wechsler, 1997) (WMS-III), and the Symbol-Digit Modalities Test (Smith, 1991) (SDMT). **Executive function**—the Categorical Verbal Fluency test (animals, vegetables, fruits), the Design Fluency test (Delis et al., 2001), and the Trial Making Test B (Reitan and Wolfson, 1985) measured the ability to select, suppress, and manipulate information. **Attention**—the Digit Span (forward and backward) component from the Wechsler Memory Scale III (Wechsler, 1997) and a computer based Spatial Span task (forward and backward) assessed attention. **Verbal memory**—the Rey Auditory Verbal Learning Test (Lezak et al., 2004) (RAVLT), a 15-item word list involving components of immediate and delayed recall, measured verbal memory. **Visuospatial memory**—a computer based Visual Paired Associates test assessed immediate and delayed recall of patterns and their locations. The test battery, including all forms and computer software, was the same for all participants throughout the entire period of testing. The test procedure was standardized with written instructions to the testers and maintained the same throughout the study.

Tests were administered in either English or Mandarin according to the participant's language preference and proficiency. Individual test scores from phases three, four and five were first *z*-transformed with reference to Phase 2, and scores from Phases 2 to 5 were then converted to *T* scores (*T* score=(z-score×10)+50). For each phase, a composite score was derived for each of the five cognitive domains by averaging the *T* scores of the respective tasks. A global cognitive score was calculated by averaging the five composite scores (for further detail, see previous work (Lo et al., 2014)). *T* scores are commonly used to quantify cognitive performance in neuropsychological studies that include multiple cognitive measures (Ferrie et al., 2011). This method centers the group mean at baseline at 50 with a standard deviation of 10. By avoiding negative values, this reduces confusion that may be associated with interpreting changes in *z*-scores.

2.3. MR imaging

High-resolution images of the brain were acquired using a T1-weighted multi echo magnetization prepared rapid acquisition gradient echo (MEMPRAGE) sequence with a 3 T Siemens Tim Trio system (Siemens, Erlangen, Germany). There were 192 contiguous sagittal slices with the following scanning parameters: repetition time (TR)=2530 ms, TI=1200 ms, flip angle=7°, field of view (FOV) 256 mm×256 mm, 256×256 matrix, isotropic voxel dimensions of 1.0 mm, 6 min 3 s acquisition time. Automated measurements of brain volumes were standardized across phases and performed using the longitudinal stream in FreeSurfer 5.1.0 (Reuter et al., 2012). Within-subject templates were estimated from individual participants images in Phase 2, 3, and 4. Common information from the template was then used to initialize subsequent processing steps to improve precision and reduce variability.

Here, we report findings regarding brain volumes which include total cerebral, gray and white matter, hippocampal, and ventricular volumes, as well as gray and white matter volumes partitioned according to frontal, parietal, temporal, and occipital lobes. Estimated total intracranial volume (Buckner et al., 2004; Jack et al., 1989) (eTIV) was used as a covariate in all correlational analyses involving brain variables to compensate for inter individual differences in head size.

2.4. Statistical analyses

We used the following mixed-effects model in SAS® 9.3 (SAS Institute, Cary NC) to quantify the annual change in brain volume and cognitive performance at both group and individual levels.

$$y_{ij}=\beta_0+\beta_1 Interval_{ij}+b_{0i}+b_{1i}Interval_{ij}+\varepsilon_{ij} \quad (1)$$

In this equation, y_{ij} is either the brain volume or the cognitive domain score for the *i*th participant on the *j*th follow-up visit. β denotes fixed effects estimates, while *b* denotes participant-specific random-effects estimates, and ε is the residual error. Interval, i.e. the time elapsed from Phase 2 (in years), was included as the independent variable, with covariance structure specified as unstructured. Time elapsed, together with the brain or cognitive measure at baseline, were included as random effects. This model captured the average longitudinal change across the participants, taking into account participant specific longitudinal effects. β_1 denotes the group mean for changes in either the brain or cognitive measures. We employed Bayesian estimates of slopes for each participant ($\beta_1 + b_{1i}$) in order to estimate individual longitudinal effects, i.e. annual changes in brain volume and cognitive function respectively.

In order to explore possible non-linear relationships with age, in a second model, we included the Interval (Cassarino and Setti, 2015) term (squared value of time elapsed from phase 2) into the mixed model analyses as a second independent variable.

$$y_{ij}=\beta_0+\beta_1 Interval_{ij}+\beta_2 Interval_{ij}^2+b_{0i}+b_{1i} Interval_{ij}+b_{2i} Interval_{ij}^2+\varepsilon_{ij} \quad (2)$$

While the first model examined linear longitudinal change across participants by taking into account linear group changes and linear individual changes, the second model allowed for examination of possible non-linear relationships. However, as we did not find any significant non-linear age effects, we did not pursue this line of investigation and employed estimates based on the first model in all subsequent analyses.

Annual percentage change (APC) values were derived from Model 1 and are estimates of individual linear longitudinal trajectories. APC for each individual was calculated by dividing the slope of each individual's brain structural measure or cognitive score by the intercept (i.e. *y* when time elapsed is zero), and multiplied by 100. We excluded six APC values which were >3 SD from the mean (one ventricular, two hippocampal, two gray matter, and one visuospatial).

Next, partial correlations were performed with SPSS® 21.0 (IBM, Chicago, IL, USA) to investigate the relationships between longitudinal changes in cognitive function and brain volume after controlling for eTIV, age, BMI, education, gender, and blood pressure (systolic and diastolic). These covariates were derived from the baseline phase (i.e. Phase 2). To illustrate the significant partial correlations, we derived the residual of the brain and the cognitive variable not accounted for by the covariates in multiple regression analyses. Residual of the cognitive variable was then plotted against that of the brain variable in scatterplots. We used repeated-measures ANCOVA and to examine whether the rate of gray and white matter atrophy varied significantly across the frontal, parietal, temporal, and occipital lobes after partialing out the contribution of the aforementioned covariates.

3. Results

3.1. Characteristics of the study sample

The current sample comprised 111 relatively healthy older adults with a mean baseline age of 67.1 years (SD=6.2 years; Table 1) and with no known active major medical conditions other than treated, uncomplicated hypertension (32.4% at baseline) or diabetes mellitus (9.9% at baseline). Participants had an average of 12.3 years of education (SD=3.1 years) and 24.3% had 15 or more years of education, making this sample relatively well educated compared to their peers. For comparison, the national average for Singapore citizens above 55 years of age who attained at least 15 years of education (i.e. university) was recorded as 3.3% in 2005 (www.singstat.gov.sg). To contribute to the analyses presented here, participants had to consistently attain MMSE scores of ≥26 in all phases.

To check for possible sampling bias, we compared demographics variables of participants included in this analysis with participants who withdrew after one phase, and thus not included in any analysis despite being relatively healthy. Participants were matched on all characteristics except on diastolic blood pressure and hypertension, where those who withdrew after the first phase had a higher diastolic blood pressure (81.0 mm Hg versus 77.6 mm Hg, p=0.01) and greater percentage of individuals suffering from hypertension (48.7% versus 32.4%, p=0.03; Supplementary Table 1).

Table 1
Sample characteristics at baseline (N=111).

	Mean/%	SD
Age, years	67.1	6.2
Follow up, years	4.8	1.5
Women, %	51.4	–
Education, years	12.3	3.1
BMI, kg/m^2	23.3	2.9
Systolic BP, mm Hg	132.0	15.0
Diastolic BP, mm Hg	77.6	9.2
Hypertension, %	32.4	–
Diabetes, %	9.9	–
APOE ε4 heterozygotes, %	19.8	–
MMSE score	28.3	1.3
GDS score	1.1	1.1
Current smoker	0.0	–
Consumes alcohol daily	0.0	–

SD, standard deviation; BMI, Body Mass Index; BP, Blood Pressure; MMSE, Mini Mental State Exam; GDS, Geriatric Depression Scale.

3.2. Estimation of non-linear effects

No significant *non-linear* effects were observed for both brain structural (p values ranging from 0.16 to 0.51) and cognitive variables (p values ranging from 0.18 to 0.99) in Model 2. Inclusion of the squared interval term in the second model did not alter statistical significance for variables found to show significant aging effects in Model 1.

3.3. Age-related changes in brain volumes

All brain structures investigated showed significant annual volumetric decline (Fig. 1A-D; see Supplementary Figs. 1 and 2 for visualization of the raw data) from −0.53%/year to −0.94%/year, and ventricles showed significant annual expansion at 3.56%/year (Fig. 1E; Table 2). Our sample demonstrated annual atrophy rates of −0.56% for total cerebral volume and −0.94% for hippocampal volume. Significant inter individual differences in these structural changes over time were observed, particularly with white matter atrophy and ventricular expansion (Supplementary Figs. 3 and 4).

Partitioning gray and white matter volumes into frontal, parietal, temporal and occipital lobes (Fig. 1F-M), we found that all gray and white matter lobar regions investigated showed significant annual decline (−0.44%/year to −0.71%/year; Table 2). The degree of annual decline (cm^3/year) differed significantly across white matter lobar regions (F=3.18, p=.024) such that atrophy in the frontal regions was greater than that in the temporal areas, followed by parietal and occipital regions (all $p < .05$). Annual volumetric decline (cm^3/year) did not significantly differ for gray matter lobar regions (F= 0.64, p=.589). However, with annual percentage change (APC; %/year), we found significant differences between lobar volumes for both gray (F=6.30, $p < .0001$) and white matter (F=6.18, $p < .0001$). For *both* gray and white matter areas, temporal lobes showed greatest annual percentage decline, followed by occipital, parietal and frontal lobes in that order (all $p < 0.05$).

3.4. Age-related changes in cognitive performance

Global cognition, denoted by an average of domain scores, did not show significant decline (−0.09%/year, p=.461; Table 2; Fig. 2A; see

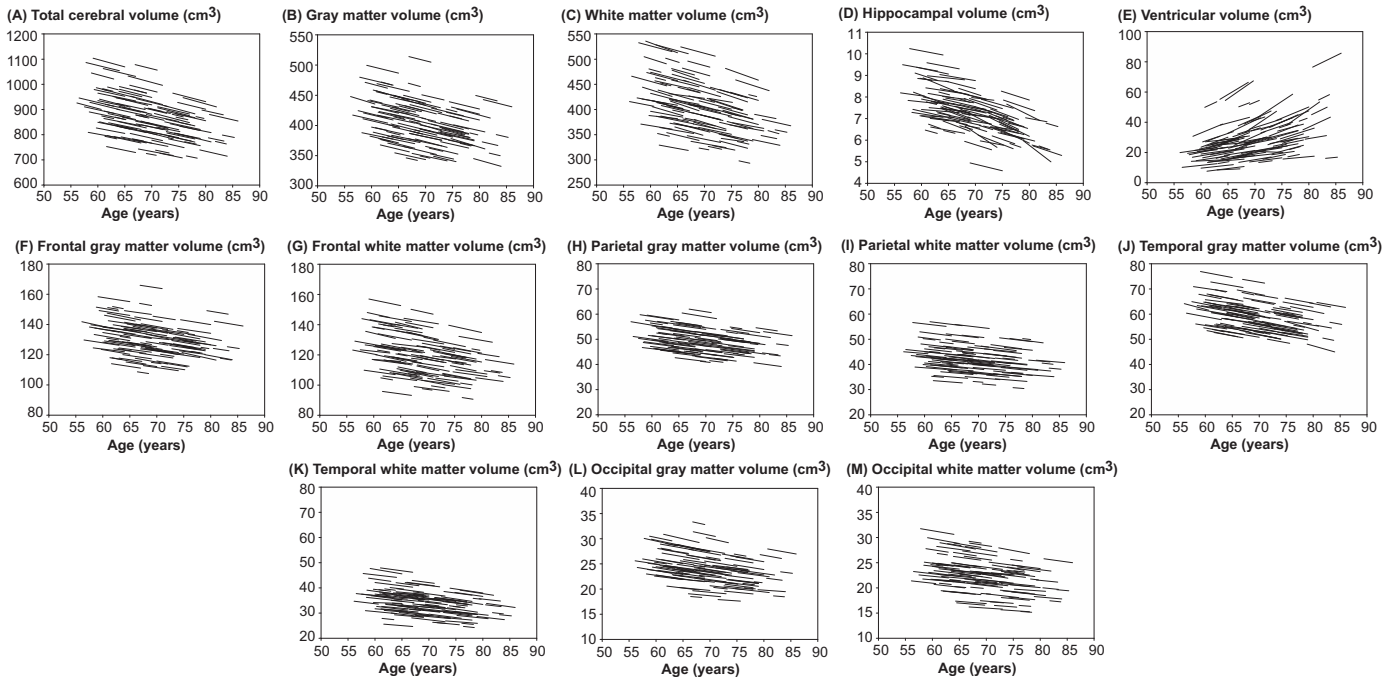

Fig. 1. Individual trajectories for five brain volume measures as well as gray and white matter volume in each lobar region; (A) total cerebral volume, (B) gray matter volume, (C) white matter volume, (D) hippocampal volume, (E) ventricular volume, (F, G) frontal, (H, I) parietal, (J, K) temporal, and (L, M) occipital. All volumes are in cm^3. (2-column fitting image).

Table 2
Annual change in brain volume and neuropsychological performance.

	Annual change				
	Mean	**SE**	***p***	**APC (%)**	**SE (%)**
Brain volume change (cm^3/year)					
Total cerebral	−4.86	0.17	< 0.001	−0.56	0.00
Gray matter	−2.14	0.14	< 0.001	−0.64	0.00
Frontal	−0.57	0.06	< 0.001	−0.44	−0.04
Parietal	−0.29	0.02	< 0.001	−0.58	−0.05
Temporal	−0.39	0.05	< 0.001	−0.66	−0.06
Occipital	−0.16	0.03	< 0.001	−0.63	−0.06
White matter	−2.63	0.10	< 0.001	−0.53	0.01
Frontal	−0.62	0.02	< 0.001	−0.51	−0.05
Parietal	−0.22	0.01	< 0.001	−0.51	−0.05
Temporal	−0.24	0.01	< 0.001	−0.71	−0.07
Occipital	−0.12	0.01	< 0.001	−0.54	−0.05
Hippocampus	−0.07	0.00	< 0.001	−0.94	0.04
Ventricles	0.94	0.06	< 0.001	3.56	0.11
Neuropsychology T score change (T/year)					
Global cognition	−0.05	0.01	0.46	−0.09	0.03
Speed of processing	−0.51	0.05	< 0.001	−0.92	0.10
Executive function	0.04	0.01	0.63	0.07	0.02
Attention	0.01	0.02	0.88	−0.01	0.03
Verbal memory	0.24	0.02	0.07	0.47	0.03
Visuospatial memory	0.00	0.00	0.98	0.01	0.00

SE: standard error.
APC: annual percentage change.

Figure Supplementary Fig. 5 for visualization of the raw data). However, speed of processing revealed a significant age-related decline (−0.92%/year, $p < .001$; Fig. 2B). Executive function (Fig. 2C), attention (Fig. 2D), verbal memory (Fig. 2E), and visuospatial memory (Fig. 2F) were relatively preserved with increasing age (−0.01 to 0.47%/year; Table 2). A fair amount of inter-individual differences in aging related changes (over time) was observed, particularly in the speed of processing domain (Supplementary Fig. 6).

3.5. Associations between longitudinal changes in brain volume and cognitive function

APC values were used in this analysis as they take into account baseline volume of each region. Associations between these longitudinally derived annual percentage changes (APC, %) in brain volume and cognitive domains are summarized in Table 3 (corresponding analyses with annual mean changes are presented in Supplementary Table 3). After adjusting for eTIV, age, BMI, education, gender, and systolic and diastolic blood pressure, poorer global cognition over time was associated with total cerebral (partial r=0.35, $p < .001$, Fig. 3A), gray matter (partial r=0.35, $p < .001$, Fig. 3B), and hippocampal volume loss over time (partial r=0.21, p=.04, Fig. 3C). Greater total cerebral atrophy was associated with significantly faster decline in verbal memory (partial r=0.24, p=.02; Fig. 3D), likely driven by the latter's positive association with white matter atrophy (partial r=0.20, p=.049, Fig. 3E). Hippocampal atrophy as well as ventricular expansion was associated with aging related decline in verbal memory (partial r=0.21; p=.03, Fig. 3F, partial r=−0.22; p=.03, Fig. 3G) and executive function (partial r=0.22, p =.03, Fig. 3H, partial r=−0.23, p =.02, Fig. 3I).

In addition, greater frontal (partial r=0.31; p=.001, Fig. 4A), parietal (partial r=0.26; p=.008, Fig. 4B) and temporal (partial r=0.30; p=.002, Fig. 4C) lobar gray matter atrophy were significantly associated with poorer global cognition). This relationship was reversed for occipital gray matter (partial r=−0.20; p=.048, Fig. 4D). Lastly, greater frontal and parietal white matter atrophy were significantly associated with faster decline in verbal memory performance (partial r =0.26; p =.008, Fig. 4E, partial r =0.31; p =.002, Fig. 4F).

Lastly, in view of the concern that blood pressure may be normalized by medication and may not reflect longer-term effects of hypertension, we included a categorical covariate of hypertension diagnosis as an additional covariate, and compared these results with the existing findings. Notably, we found that results remained the same, whereby

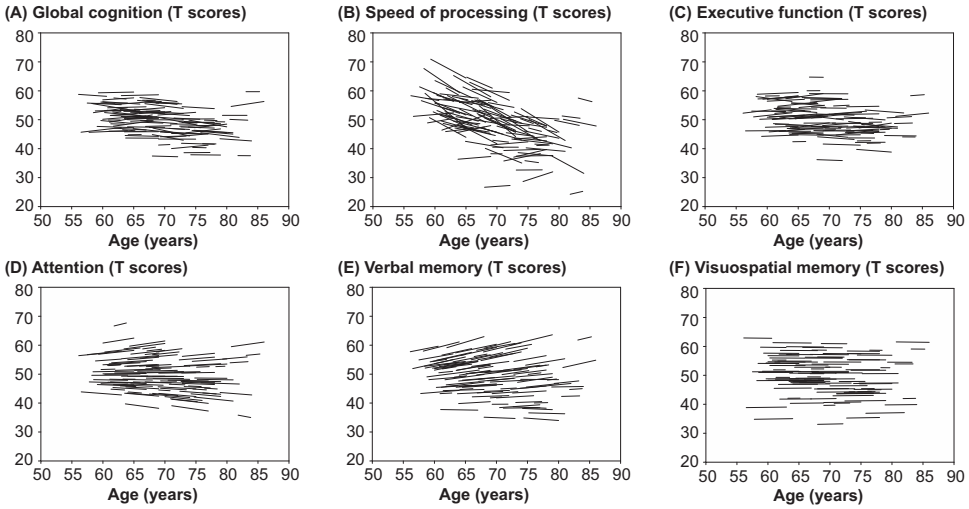

Fig. 2. Individual trajectories for cognitive performance; (A) global cognition, (B) speed of processing, (C) executive function, (D) attention, (E) verbal memory, (F) visuospatial memory. Performance is measured in T scores. (2-column fitting image).

significant associations found earlier remained significant (see Supplementary Table 4).

4. Discussion

The present longitudinal study tracked the changes in brain volume and cognitive function among relatively healthy East-Asian older adults over 8 years. The present data are valuable for a number of reasons. Firstly, multi-occasion longitudinal data allows for an understanding of the time course of brain and cognitive changes. Secondly, an examination of aging-related changes in a relatively healthy cohort benefits both an understanding of healthy aging as well as that of abnormal cognitive decline because quantifying changes in normal aging provides a basis for comparing pathological cognitive decline. Thirdly, longitudinal data from an East Asian cohort that comprises both structural imaging as well as neuropsychological data is unique when most of our present knowledge on brain aging is from Western samples.

Our results showed volumetric decline for all measures of brain parenchyma examined, as well as ventricular expansion with increasing age. In contrast, speed of processing was the only cognitive domain affected by aging in this relatively well-educated cohort, while performance in other cognitive domains was maintained. After controlling for eTIV, demographic and health variables, we found total cerebral volume loss to be associated with verbal memory decline, an effect likely driven by the loss of white matter, specifically in frontal and parietal regions. In addition, hippocampal atrophy as well as ventricular expansion were associated with greater decline in verbal memory and executive functions.

4.1. Estimation of non-linear effects

While other studies have found non-linear effects on brain structure with aging, we did not find any non-linear age effects in our sample. One reason for this may be the relatively narrow age range and smaller sample size in our study as compared to others that examine non-linear changes. For example, Fjell et al. (2013) examined 1100 adults across 18–94 years in a cross-sectional analysis and 142 adults ranging from 60–91 years in a longitudinal analysis. In their work, they found that non-linear aging was observed by comparing the period before and after 60 years of age. They observed stable hippocampal volume, followed by linear decline. Additionally, total brain volume showed steeper linear decline after the age of 60 years (Fjell et al., 2013). As our sample included few people below the age of 60, the relatively narrow age range in our sample may have precluded detection of non-linear trajectories. In addition, it must be emphasized that not every participant had 4 data points over 8 years. Of the 111 older adults

Table 3
Correlations between annual percentage change (APC, %) of brain volume and cognitive function.

	Global cognition	Speed of processing	Executive function	Attention	Verbal memory	Visuospatial memory
TCV	0.35***	0.01	0.15	0.12	0.24*	−0.05
Gray Matter	0.35***	0.01	0.12	0.10	0.07	−0.04
Frontal	0.31***	0.02	0.01	0.04	0.01	0.05
Parietal	0.26**	−0.01	0.09	0.13	0.05	−0.10
Temporal	0.30**	0.02	0.08	0.13	0.02	−0.05
Occipital	−0.20*	−0.06	−0.14	−0.05	−0.10	0.02
White Matter	0.05	−0.03	0.06	0.07	0.20*	−0.05
Frontal	0.02	−0.04	0.03	0.06	0.26**	−0.06
Parietal	0.19	0.05	0.13	−0.03	0.31**	−0.03
Temporal	−0.00	0.05	0.08	0.02	0.09	−0.04
Occipital	0.01	−0.00	0.01	−0.03	−0.01	0.01
HC	0.21*	0.05	0.22*	0.06	0.21*	−0.18
Ventricles	−0.17	−0.03	−0.23*	−0.03	−0.22*	0.15

TCV, Total cerebral volume; GM, gray matter; WM, white matter; HC, hippocampus
Adjusted for eTIV, age, BMI, education, gender, and systolic and diastolic blood pressure.
* $p < .05$.
** $p < .01$.
*** $p < .001$.

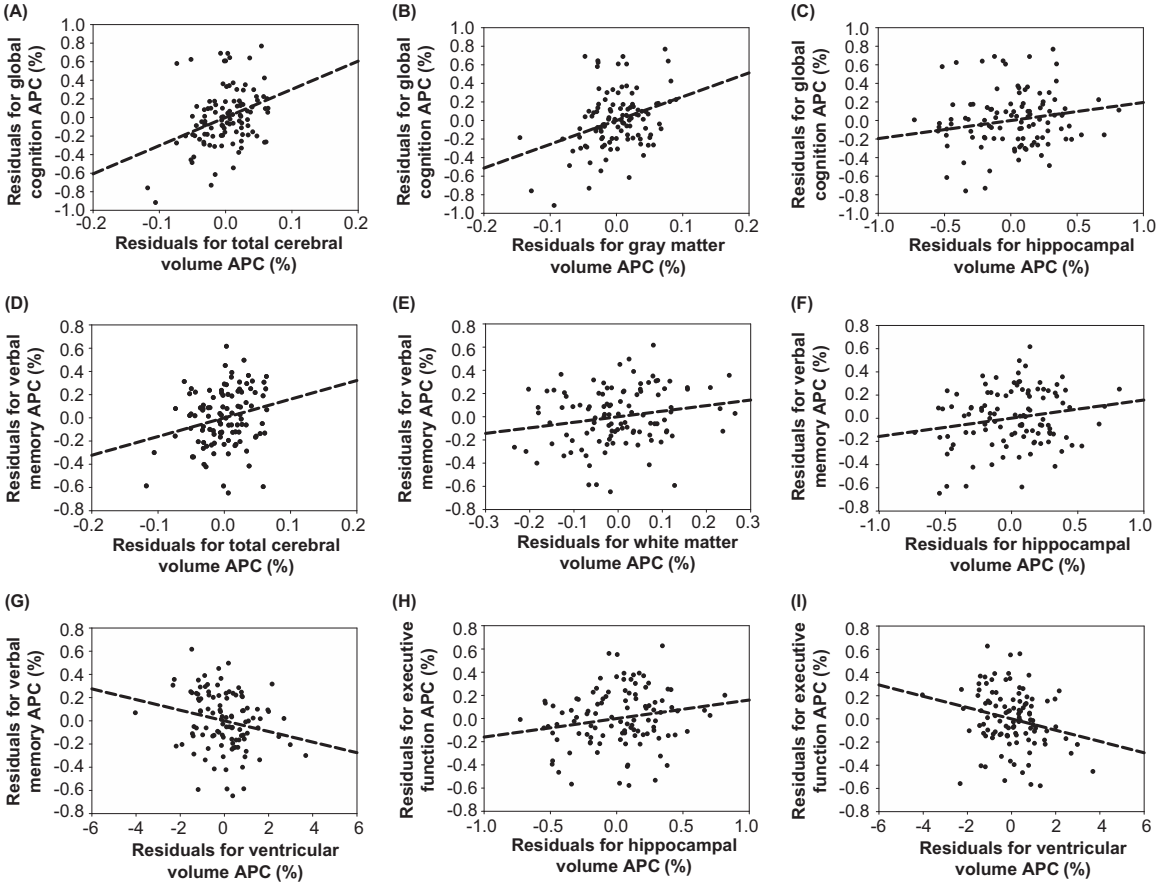

Fig. 3. Scatterplots illustrating significant associations between brain and cognitive aging. Plotted here are the unstandardized residuals for annual percentage changes (APC) in cognitive and brain measures after partialing out effects of eTIV, age, BMI, education, gender, and blood pressure. Faster decline in global cognition was associated with accelerated (A) total cerebral, (B) gray matter, and (C) hippocampal volume loss. (D) Faster total cerebral volume loss was associated with faster deterioration in verbal memory, possibly driven by the latter's significant association with (E) degree of white matter volume loss. Greater hippocampal atrophy as well as ventricular expansion was associated with (F, G) more rapid decrease in verbal memory and (H, I) executive function. (2-column fitting image).

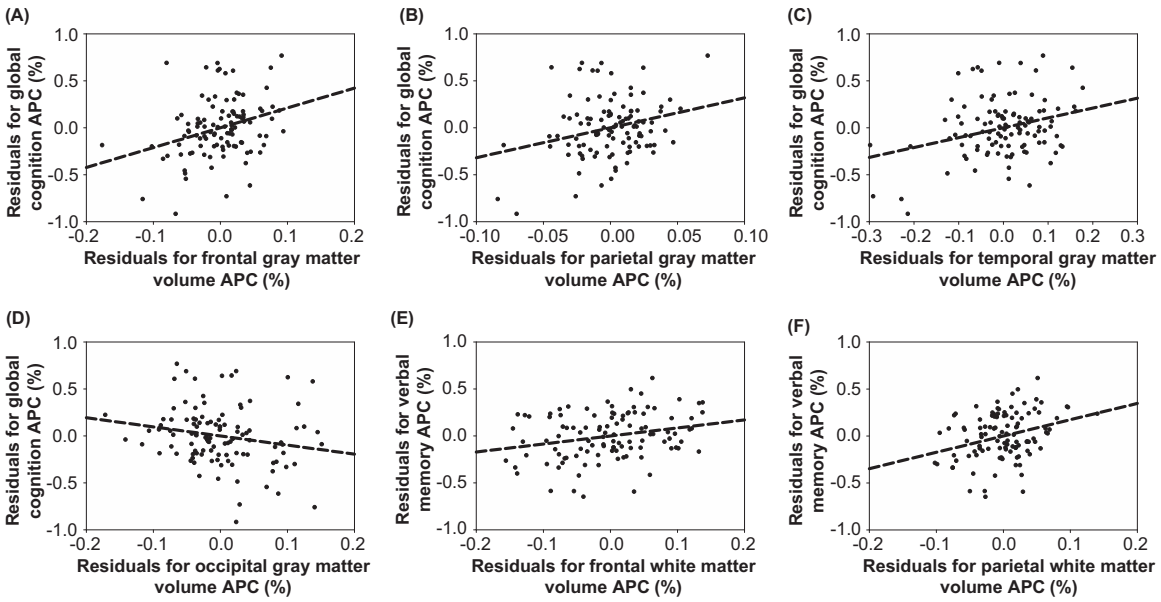

Fig. 4. Scatterplots illustrating significant associations between loss of gray and white matter lobar volumes and decrease in cognitive function. Plotted here are the unstandardized residuals for annual percentage changes (APC) in cognitive performance as well as gray and white matter lobar volumes,after partialing out effects of eTIV, age, BMI, education, gender, and blood pressure. Faster decline in global cognition was associated with more rapid loss in gray matter volume in (A) frontal, (B) parietal, and (C) temporal regions. (D) This relationship was reversed for the occipital lobe. Faster white matter atrophy in (E) frontal and (F) parietal regions was significantly associated with faster decline in verbal memory. (2-column fitting image).

who participated, 24 had two time points, 25 had three time points, and 62 had four time points. These factors may have contributed to failure to detect non-linear longitudinal changes in brain structure.

These observations notwithstanding, it should be noted that we recently found a u-shaped trajectory for functional connectivity measures in a sample from our S-LABS cohort (Ng et al., 2016), suggesting that brain functional measures may be more sensitive to non-linear effects.

4.2. Age-related changes in brain structures

In healthy aging, cortical atrophy and ventricular dilation generally begin to occur around 30 to 40 years of age (Walhovd et al., 2005), followed by a relatively stable age-related decline. Notably, it is often the rate of change that distinguishes healthy aging from pathological aging (Apostolova et al., 2012; Roussotte et al., 2014). *The rate of change* of several brain morphometry metrics estimated from our relatively healthy, Chinese, older adult cohort is similar to estimates from the West. Total cerebral volume was found to change at a rate of −0.56%/year, a rate comparable to other Western longitudinal studies examining healthy aging (−0.5% (Jack et al., 2005); −0.55% (Enzinger et al., 2005)). In our study, the hippocampus was found to have the largest annual decline (−0.94%) among the structures investigated. A recent meta-analysis (Fraser et al., 2015) reported a comparable hippocampal atrophy rate (−0.98%) for healthy older adults aged between 55 to 70 years. Annual rate of ventricular dilation at 3.56%/year was also similar to what has been found in Caucasian healthy older adults (3.85% (Madsen et al., 2015), 4.3% (Mak et al., 2015)). Despite differences in diet, lifestyle and culture, the present results extend to the longitudinal domain, reinforcing previous cross-sectional reports (Chee et al., 2011; Chee et al., 2009) that found no noteworthy differences in the longitudinal changes in whole brain volumes between healthy older East Asians and their predominantly Caucasian participants.

Comparisons for lobar measures of brain structure were more difficult due to methodological differences in how these measurements were derived. Reported annual rates of gray matter decline (cm^3/year) range from −0.56 to −1.05 in frontal regions, −0.43 to −0.55 in temporal regions, −0.21 to −0.90 in parietal regions, and −0.33 to −0.36% in occipital regions (Resnick et al., 2003; Driscoll et al., 2009; Jernigan et al., 2001). Rates of decline in our sample were lower than Western estimates for occipital gray matter regions (−0.16 cm^3/year), and slightly lower for temporal gray matter regions (−0.39 cm^3/year).

For lobar changes in white matter, annual rates of decline in our sample were generally lower than that found in healthy Western samples, particularly for temporal and parietal regions. While studies done in Western societies report declines of −0.33 to −0.68 cm^3/year for parietal white matter regions and −0.45 to −1.56 cm^3/year for temporal white matter regions (Resnick et al., 2003; Driscoll et al., 2009; Jernigan et al., 2001), our study found annual declines of −0.22 cm^3/year and −0.24 cm^3/year respectively.

As seen in our data, and noted by others, aging related brain structural changes are heterogeneous (Fjell et al., 2013; Walhovd et al., 2005) across individuals as well as topographical region. This indicates utility in delineating normative values for various structures in order to better differentiate healthy from abnormal aging related changes.

It is worth highlighting that patterns of structural decline observed with measures of volumetric decline (cm^3/year) and annual percentage change (APC, %) differ (see Table 2). APC takes into account the baseline volume of each structure in order to normalize change across structures or samples, the latter being particularly beneficial for meta-analytic reviews (Fraser et al., 2015). In studies that present both measures, discrepancies between the two measures may be observed (Chee et al., 2009; Krueger et al., 2010).

4.3. Age-related changes in cognitive function

We found a marked aging effect on speed of processing, whereas attention, executive function, verbal and visuospatial memory were relatively preserved. This is consistent with the robust longitudinal decline in speed of processing portrayed in existing literature (Salthouse, 2011). Performance maintenance in the other cognitive domains likely reflects the superior cognitive health of our sample, criteria for inclusion into analyses (e.g. MMSE ≥ 26 in all phases), and practice effects. Practice effects likely explain the trend toward improvement in verbal memory over time in our sample. A similar pattern of improvement in verbal memory has also been observed in previous longitudinal studies (Goh et al., 2012) and indicates the difficulty in estimating the true rate of cognitive decline in domains where repeated testing masks genuine aging related decline.

Of particular interest in a region where there is high growth in the number aged persons, is how to estimate the efficacy of cognitive interventions aimed at maintaining or improving cognitive performance in old age. As the conceptualization of what constitutes successful cognitive aging continues to evolve (Cosco et al., 2014), a solid basis of comparison is needed for the effective evaluation of interventions. Many contemporary studies are hampered by uncertain quality of their estimates of the time course of training-dependent cognitive changes (Brehmer et al., 2014). The present study should provide valuable reference data for deriving effect sizes of the benefits of cognitive interventions over time.

4.4. Associations between longitudinal changes in brain volume and cognitive function

We found longitudinal associations between total cerebral volume loss and verbal memory decline, which appear to be driven by the association with white matter loss, particularly in the frontal and parietal regions. Compared to temporal and occipital regions, frontal and parietal regions may be more sensitive to the effects of aging on cognition (Resnick et al., 2003).

An early imaging study involving older adults, found that white matter lesions were associated with poorer recall of word lists (Breteler et al., 1994). Subsequent studies have found white matter disruption to associate with poorer verbal memory in both healthy (Charlton et al., 2013) and cognitively impaired older adults (Delano-Wood et al., 2012). Notably, a recent study examining white matter and memory in healthy adults over 2 years found that improvement in memory was associated with better connectivity in frontal white matter (Bender et al., 2015).

We found hippocampal atrophy to be linked to verbal memory decline. A number of studies, cross-sectional and longitudinal, have documented the association between hippocampal atrophy and verbal memory in both healthy (Chee et al., 2011; Kramer et al., 2007; Cardenas et al., 2011) as well as cognitively impaired elderly (Henneman et al., 2009; Petersen et al., 2000). Longitudinal associations between ventricular expansion and verbal memory were also found in the present study. In healthy elderly, ventricular expansion has been linked to declines in general cognition as well as in specific domains such as verbal and executive function (Breteler et al., 1994; Carlson et al., 2008; Palm et al., 2009).

Perhaps obliquely related to verbal memory, our study also found associations between hippocampal atrophy and ventricular enlargement with executive function. Executive function encompasses processes thought to be necessary for successful retrieval of information, required in most verbal memory tasks (Salthouse et al., 2003; Crawford et al., 2000; Stuss and Alexander, 2000). For example, the categorical fluency test, a component of executive function in our study (see Section 2), involves retrieval of object names within specified categories.

Similar to other cross-sectional and longitudinal studies, we found gray matter atrophy, particularly in the frontal, parietal, and temporal regions, to be associated with faster decline in overall global cognition (Tisserand et al., 2004; Staff et al., 2004). Gray matter atrophy is associated with poorer cognitive function in both healthy older adults and groups with a range of cognitive impairments (Fleischman et al., 2014; Arvanitakis et al., 2015; Vaughan et al., 2014).

Despite its strong association with age and aging, we did not find any association of speed of processing with the brain structures investigated here. However, in a related sample from the same cohort of older adults, we found decline in speed of processing to be associated with age-related reductions in white matter fractional anisotropy (Hong et al., 2015). Also in the same cohort, faster decline in speed of processing with aging was associated with greater loss of functional segregation between the executive control network and the default mode network (Ng et al., 2016).

4.5. Limitations

The age range in this study is relatively narrow, as we only tracked brain and cognitive changes from 55 years onwards. Future studies should include a wider age range so as to establish any correlation between volumetric brain changes in young adulthood and mid-age with adverse cognitive changes later in life. In addition, this may also benefit examination of non-linear longitudinal age effects.

Other limitations concern image processing. It has been suggested that FreeSurfer's estimates of hippocampal volume may be biased in aging populations (Wenger et al., 2014), but it is unclear how this may impact longitudinal estimates of hippocampal atrophy. In addition, as we examined total ventricular volume only, we were unable to explore differential patterns of aging within the ventricular system.

Lastly, as many distinct correlations were performed to examine longitudinal brain-cognition relationships, caution should be exercised in generalizing from these results in the light of the multiple comparisons made.

5. Conclusions

All measures of brain parenchyma investigated showed significant atrophy, while expansion of the ventricles was observed. Speed of processing was the only cognitive domain that showed significant age-related decline. In addition, the extent of brain aging was associated with the decline in cognitive function. Our findings on an East Asian cohort of healthy elders contribute to the growing body of longitudinal studies investigating aging-related changes in neurobiology and cognition.

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Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.neuroimage.2016.10.016.

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