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

Ruth L.F. Leong, June C. Lo, Sam K.Y. Sim, Hui Zheng, Jesisca Tandi, Juan Zhou, Michael W.L. Chee*

Centre for Cognitive Neuroscience, Neuroscience and Behavioral Disorders Program, Duke-NUS Medical School, Singapore

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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

* Correspondence to: Centre for Cognitive Neuroscience, Duke-NUS Medical School, 8 College Road, Level 6, 169857, Singapore.
E-mail address: michael.chee@duke-nus.edu.sg (M.W.L. Chee).

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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.

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