NeuroImage 86 (2014) 203–211

Contents lists available at ScienceDirect

NeuroImage

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

A longitudinal study of brain atrophy over two years in community-dwelling older individuals

Jiyang Jiang [a], Perminder Sachdev [a,b], Darren M. Lipnicki [a], Haobo Zhang [a], Tao Liu [a], Wanlin Zhu [c], Chao Suo [a], Lin Zhuang [a], John Crawford [a], Simone Reppermund [a], Julian Trollor [a,d], Henry Brodaty [a,e,f], Wei Wen [a,b,*]

[a] Centre for Healthy Brain Ageing (CHeBA), School of Psychiatry, University of New South Wales, Sydney, NSW, Australia
[b] Neuropsychiatric Institute, Prince of Wales Hospital, Randwick, NSW, Australia
[c] State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University, Beijing, China
[d] Department of Development Disability Neuropsychiatry, School of Psychiatry, University of New South Wales, Sydney, NSW, Australia
[e] Aged Care Psychiatry, Prince of Wales Hospital, Randwick, NSW, Australia
[f] Dementia Collaborative Research Centre, University of New South Wales, Sydney, NSW, Australia

ARTICLE INFO

Article history:
Accepted 11 August 2013
Available online 17 August 2013

Keywords:
Cortical thickness
Subcortical volume
Longitudinal
Magnetic resonance imaging
Non-demented

ABSTRACT

Most previous neuroimaging studies of age-related brain structural changes in older individuals have been cross-sectional and/or restricted to clinical samples. The present study of 345 community-dwelling non-demented individuals aged 70–90 years aimed to examine age-related brain volumetric changes over two years. T1-weighted magnetic resonance imaging scans were obtained at baseline and at 2-year follow-up and analyzed using the FMRIB Software Library and FreeSurfer to investigate cortical thickness and shape and volumetric changes of subcortical structures. The results showed significant atrophy across much of the cerebral cortex with bilateral transverse temporal regions shrinking the fastest. Atrophy was also found in a number of subcortical structures, including the CA1 and subiculum subfields of the hippocampus. In some regions, such as left and right entorhinal cortices, right hippocampus and right precentral area, the rate of atrophy increased with age. Our analysis also showed that rostral middle frontal regions were thicker bilaterally in older participants, which may indicate its ability to compensate for medial temporal lobe atrophy. Compared to men, women had thicker cortical regions but greater rates of cortical atrophy. Women also had smaller subcortical structures. A longer period of education was associated with greater thickness in a number of cortical regions. Our results suggest a pattern of brain atrophy with non-demented people that resembles a less extreme form of the changes associated with Alzheimer's disease (AD).

Introduction

To appreciate the differential effects of neurodegenerative disorders such as AD on rates of brain atrophy, it is important to document changes in brain structures associated with aging in the absence of dementia. With greater sensitivity (Ridha et al., 2006) and more power (Fox et al., 2000; Hua et al., 2009) to detect anatomical changes than cross-sectional studies, longitudinal studies of the aging brain are of increasing interest, and are now facilitated by large open access databases such as the Alzheimer's Disease Neuroimaging Initiative (ADNI) (Mueller et al., 2005) and the Open Access Series of Imaging Studies (OASIS) (Marcus et al., 2010).

Commonly, previous longitudinal studies have focused on changes in specific structures, reporting atrophy rates of −1.55% to −0.8% per year for the hippocampus (Barnes et al., 2009; Du et al., 2004, 2006; Fjell et al., 2009a; Jack et al., 1998) and −1.4% to −0.55% per year for the entorhinal cortex in normal aging individuals aged 58–91 years (Du et al., 2003, 2004, 2006; Fjell et al., 2009a), and expansion rates of 3.0% to 4.2% per year of the ventricles in individuals aged 60–95 years (Carlson et al., 2008; Driscoll et al., 2009; Fjell et al., 2009a; Jack et al., 2009; Schuff et al., 2010). A few studies have investigated more comprehensive regions of interest, but were limited by small sample sizes (Driscoll et al., 2009; Fjell et al., 2009a). Methodological limitations and contradictory results make it unclear as to how brain atrophy changes with age, i.e. whether it accelerates (Driscoll et al., 2009; Fjell et al., 2009a; McDonald et al., 2009; Scahill et al., 2003; Walhovd et al., 2005), accelerates to a plateau (Schuff et al., 2010), or remains relatively constant (Allen et al., 2005; Fjell et al., 2009b; Jack et al., 2008).

Age-related structural brain changes may also be affected by demographic factors such as sex and education. Previous studies investigating these factors have produced inconsistent results. For example, in individuals aged 15 to 80 years, men were found to have larger cortical gray matter (GM) (Carne et al., 2006) and subcortical (Goldstein et al.,

* Corresponding author at: Centre for Healthy Brain Ageing (CHeBA), School of Psychiatry, University of New South Wales, NPI, Euroa Centre, Prince of Wales Hospital, Randwick, NSW 2031, Australia. Fax: +61 2 9382 3774.
E-mail address: w.wen@unsw.edu.au (W. Wen).

1053-8119/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.neuroimage.2013.08.022

2001; Raz et al., 2004) volumes than women after adjusting for different brain sizes in some cross-sectional studies, but not in others (Mechelli et al., 2005; Sowell et al., 2007). Studies focusing on early and middle adulthood have yielded similar contradictory results (Allen et al., 2003; Goldstein et al., 2001; Luders et al., 2006; Raz et al., 2004; Rijpkema et al., 2012). Amongst older individuals, aged 67 to 75, men showed a greater loss of gray matter than women in temporal neocortex, prefrontal cortex, and medial temporal regions (Curiati et al., 2009). However, one longitudinal study found that women had higher atrophy rates than men (Hua et al., 2010). In terms of education, some cross-sectional studies have found that larger brain structures are associated with greater number of years of education (Liu et al., 2012; Piras et al., 2011; Sole-Padulles et al., 2009), whereas others have reported opposing results (Coffey et al., 1999; Fotenos et al., 2008). Effects of education on age-related changes in brain structures do not appear to have been addressed in a longitudinal study.

The aim of the present study was to use longitudinal data to comprehensively investigate late-life changes in brain structures associated with aging, and the extent to which these are affected by sex and education. We hypothesized that the majority of brain regions would have shrunk after two years, and age, sex and education would have an impact on the severity and pattern of atrophy.

Material and methods

Participants

Participants were members of the Sydney Memory and Ageing Study (MAS), a longitudinal study of community-dwelling individuals aged 70 to 90 years recruited via the electoral roll within two regions of Sydney, Australia. Methods and measures were described in detail previously (Sachdev et al., 2010). Individuals were excluded if they had a previous diagnosis or current evidence of dementia, mental retardation, psychotic disorder including schizophrenia or bipolar disorder, multiple sclerosis, motor neuron disease, developmental disability, or progressive malignancy; or if they lacked sufficient English to complete assessments. Of 1037 participants aged 70–90 years in the study, 544 underwent an MRI scan at baseline and 425 underwent an MRI scan at the 2-year follow-up. After excluding the participants with diagnosis of dementia at follow-up, 345 participants who were scanned at both baseline and follow-up were used as the sample for the present study (demographic characteristics in Table 1, medical conditions in Supplementary Table 1). The participants included in the present study were significantly different from those who were excluded at both baseline and follow-up in terms of age (baseline: $p < 0.001$, follow-up: $p < 0.001$) and years of education (baseline: $p < 0.009$, follow-up: $p < 0.038$); the included individuals were two years younger and had received six months of more education on average. We did not find any significant difference between included and the excluded participants on the Mini Mental State Examination (MMSE) (Folstein et al., 1975) (baseline: $p < 0.418$, follow-up: $p < 0.289$), diagnostic classification (baseline: $p < 0.705$, follow-up: $p < 0.482$), or female/male proportion ($p < 0.218$).

The study was approved by the Human Research Ethics Committees of the University of New South Wales and the South Eastern Sydney and Illawarra Area Health Service.

Table 1
Demographic characteristics.

	Baseline (wave 1)	Follow-up (wave 2)
Age (years)	77.91 ± 4.51 (70.48–90.40)	79.82 ± 4.50 (72.49–92.51)
Sex (male/female)	164/181	164/181
Education (years)	12.00 ± 3.65	12.00 ± 3.65
MMSE	28.77 ± 1.26 (n = 345)	28.85 ± 1.41 (n = 344)
CDR	0.066 ± 0.169 (n = 328)	0.166 ± 0.251 (n = 344)

Magnetic resonance imaging

At baseline, 171 of the 345 scans were acquired using a Philips 3 T Intera Quasar scanner (Philips Medical Systems, Best, The Netherlands) located at the Prince of Wales Medical Research Institute, Sydney. The remaining 174 baseline scans and all follow-up scans were acquired on a Philips 3 T Achieva Quasar Dual scanner. Acquisition parameters of both scanners for T1-weighted structural MRI scans were identical: TR = 6.39 ms, TE = 2.9 ms, flip angle = 8°, matrix size = 256 × 256, FOV = 256 × 256 × 190, and slice thickness = 1 mm with no gap in between, yielding $1 \times 1 \times 1$ mm^3 isotropic voxels.

The replacement of the scanner during data collection (in 2007) was due to reasons beyond the investigators' control. However, as the sample recruitment was random, little systematic sampling bias was likely to be caused by the scanner change. At baseline, the participants scanned with the two different scanners were investigated in terms of social, demographic and imaging parameters. There was no significant difference in the sex ($p < 0.443$) or years of education ($p < 0.051$) of participants undergoing scans in the two scanners. Gray matter, white matter, cerebrospinal fluid volumes and total intracranial cavity volume (ICV) of the whole brain were not significantly different between the scans of participants scanned using two different scanners after controlling for age, education and sex.

Image processing

Cortical structures were processed by FreeSurfer v5.1.0 (http://surfer.nmr.mgh.harvard.edu/). To extract reliable volume and thickness estimates, images were automatically processed with the longitudinal stream in FreeSurfer (Reuter et al., 2012). This creates an unbiased within-subject template space and image (Reuter and Fischl, 2011) using robust, inverse consistent registration (Reuter et al., 2010). Processing steps, including skull stripping, Talairach transforms, atlas registration, spherical surface maps, and parcellations were then initialized with common information from the within-subject template, significantly increasing reliability and statistical power (Reuter et al., 2012). Based on gyral and sulcal anatomy, the cortex was segmented into 34 different gyral regions per hemisphere (13 frontal, 9 temporal, 4 occipital, 7 parietal, and insula), using the Desikan–Killiany Atlas (Desikan et al., 2006). For each of these regions, mean cortical thickness was calculated as the distance (in mm) between the pial and gray/white matter surfaces.

For subcortical structures, T1-weighted data were processed with the FMRIB Software Library (FSL) v5.0.1 (Jenkinson et al., 2012; Smith et al., 2004; Woolrich et al., 2009). We used FSL rather than FreeSurfer after preliminary analyses of hippocampal volumes which revealed stronger correlations with 92 manual tracing results for FSL ($r = 0.67$ to 0.71) than for FreeSurfer ($r = 0.51$ to 0.52). FSL also allowed us to conduct subcortical vertex-wise surface analyses. The correlation between FSL generated and manually traced hippocampal volume was consistent with a previous study of 20 participants in their mid-30s ($r = 0.66$, Morey et al., 2009).

Subcortical structures were processed by first removing non-brain tissue, by warping a brain mask defined in the standard space back to the T1-weighted structural MRI scan. The brain mask was obtained with an automated skull stripping procedure based on the SPM5 skull-cleanup tool (Ashburner, 2009). We then used FMRIB's Linear Image Registration Tool (FLIRT, v5.5) (Jenkinson et al., 2002), to linearly register the follow-up brain image of each participant onto their baseline brain image. FMRIB's Integrated Registration and Segmentation Tool (FIRST v4.1) (Patenaude et al., 2011), was then used to generate 14 subcortical structures (7 per hemisphere) according to the fitted shape model.

Quality control

We conducted visual quality control of the FSL results using ENIGMA protocols (http://enigma.loni.ucla.edu/protocols/imaging-