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Variation in longitudinal trajectories of cortical sulci in normal elderly

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ABSTRACT

Sulcal morphology has been reported to change with age-related neurological diseases, but the trajectories of sulcal change in normal ageing in the elderly is still unclear. We conducted a study of sulcal morphological changes over seven years in 132 normal elderly participants aged 70–90 years at baseline, and who remained cognitively normal for the next seven years. We examined the fold opening and sulcal depth of sixteen (eight on each hemisphere) prominent sulci based on T1-weighted MRI using automated methods with visual quality control. The trajectory of each individual sulcus with respect to age was examined separately by linear mixed models. Fold opening was best modelled by cubic fits in five sulci, by quadratic models in six sulci and by linear models in five sulci, indicating an accelerated widening of a number of sulci in older age. Sulcal depth showed significant linear decline in three sulci and quadratic trend in one sulcus. Turning points of non-linear trajectories towards accelerated widening of the fold were found to be around the age between 75 and 80, indicating an accelerated atrophy of brain cortex starting in the age of late 70s. Our findings of cortical sulcal changes in normal ageing could provide a reference for studies of neurocognitive disorders, including neurodegenerative diseases, in the elderly.

Introduction

Ageing is associated with morphological changes in the brain. It has been shown that with increased age, there is a reduction of gray matter (GM) and white matter (WM) (Raz et al., 2005), a reduced GM/WM ratio (Courchesne et al., 2000), and an increase in the volume of cerebrospinal fluid (CSF) (Good et al., 2001). These changes are however not uniform in different stages of ageing, in different cortical regions or in the two cerebral hemispheres. Using measures such as regional brain volume, cortical thickness and gray matter density, it has been reported that age-related cortical atrophy is most frequently observed in the frontal (Coffey et al., 1992; Sowell et al., 2007; Fjell et al., 2010) and temporal lobes (Coffey et al., 1992; Raz et al., 2005; Sowell et al., 2003; Fjell et al., 2010). Accelerated reduction of tissue volume was found in selective regions after age of 60 (Pfefferbaum et al., 2013).

A limitation of evaluating brain changes on the basis of GM/WM segmentation is that due to changes in both T1 relaxation and proton density, the contrast between GM and WM decreases with age (Cho et al., 1997; Steen et al., 1995), thereby making the reliability of the measures of GM and WM volumes age-dependent. To obviate this problem, another approach to examine cortical change has been to measure cortical sulci. It is well known that cortical sulci widen with age, and this is possibly related to the thinning of the gyri due to reduction in gyral GM and WM (Magnotta et al., 1999; Symonds et al., 1999; Liu et al., 2013). Sulcal

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widening is commonly used by radiologists as a surrogate of cortical atrophy in the clinical setting. There have been a few systematic studies of changes in cortical sulci with age. Changes are reportedly most prominent in the central sulcus (Butman and Floeter, 2007; Good et al., 2001; Kochunov et al., 2005), Sylvian fissure (Cykowski et al., 2008; Sowell et al., 2002; Thompson et al., 1998), inferior frontal sulcus (Im et al., 2006; Kochunov et al., 2005; Nordahl et al., 2007) and superior frontal sulcus (Im et al., 2006; Kochunov et al., 2005; Liu et al., 2010; Rettmann et al., 2006). It is noteworthy that Kochunov et al. (2005) reported that with increased age, sulci widened by 0.7mm/decade and became shallower by 0.4mm/decade in the age range of 20–82. Their study was limited by the small sample size (n = 10) of those over 70 years. Since the age range of 70–90 is of particular importance to neurocognitive disorders and neurodegenerative diseases (Brodaty et al., 2013; Sachdev et al., 2010), we believe that it warrants a closer examination.

There are well-known limitations in using cross-sectional samples to study age-related changes (Lindenberger et al., 2011; Rabbitt, 2011; Raz and Lindenberger, 2011; Salthouse, 2011; Thompson et al., 2011; Nyberg et al., 2010; Rönnlund et al., 2005), in particular the confounding influence of cohort effects. To our knowledge, there have been only two studies focused on the sulcal morphology in the cognitively normal elderly. Rettmann et al. (2006) reported the decrease in surface area and sulcal depth at 4-year follow-up compared with baseline in 35 subjects aged 59–84 years. A cross-sectional study from our group (Liu et al., 2010) found an increase in sulcal widths of six prominent sulci in a much larger sample (n = 319) aged 70–90 years.

This study aims to examine the trajectories of sulcal morphological changes using longitudinal MRI data at three time points over 7 years, of the cognitively normal elderly in the age range of 70–90 years at baseline. The relatively large sample size of 132 participants with 271 scans has enabled us to investigate the pattern of cortical atrophy beyond the usual linear model and explore non-linear trajectories to better fit the fold opening and sulcal depth.

Methods

Participants

Participants were drawn from the Sydney Memory and Ageing Study (MAS), a longitudinal study of community-dwelling individuals aged 70–90 years recruited randomly via the electoral roll from the Eastern region of Sydney, Australia. At baseline, potential MAS participants were excluded if they had suffered any medical or psychiatric conditions that may have prevented them from completing assessments, a Mini-Mental State Examination (MMSE) score < 24 adjusted for age and education, or if diagnosed with dementia (for full recruitment and exclusion protocols see Sachdev et al., 2010). They were first examined between 2005 and 2007 and re-examined approximately 2, 4 and 6 years later. Participants were classified as cognitively normal if performance on all test measures was above the 6.68 percentile (−1.5 SDs) or equivalent score compared to normative published values, they were not demented and they had normal function or minimal impairment in IADLs defined by a total average score <3.0 on the Bayer ADL scale. A total of 135 participants with one or more available structural MRIs were classified as cognitively normal in all four examinations (baseline and three follow-ups, and structural MRI scans were available at baseline, 2-year and 6-year follow-up), who were then included in this study. After the removal of the scans that had failed key image processing steps such as masking, segmentation or sulcus labelling, we finally included a sample size of 132 participants with 271 scans in the study (demographic characteristics in Table 1).

Standard protocol approvals, registrations, and patient consents

The study was approved by the Ethics Committees of the University of New South Wales and the South Eastern Sydney and Illawarra Area Health Service. Written informed consent was obtained from each participant.

Table 1
Demographic characteristics.

	Baseline	Two-year follow-up	Six-year follow-up
Age (years)	76.39 ± 3.95	78.00 ± 3.77	81.89 ± 4.02
Number of subjects (male/female)	110 (44/66)	90 (33/57)	71 (30/41)
Education (years)	12.37 ± 3.63	12.09 ± 3.46	12.62 ± 3.57
MMSE score	28.82 ± 0.99	29.13 ± 0.99	28.82 ± 1.07
CDR score	0.014 ± 0.083	0.028 ± 0.115	0.056 ± 0.159

MMSE = Mini Mental State Examination.
CDR = Clinical Dementia Rating.

Image acquisition

At baseline, 59 of the 110 scans were acquired using a Philips 3 T Intera Quasar scanner (Philips Medical Systems, Best, The Netherlands) located at the Neuroscience Research Australia (NeuRA) in Sydney, Australia. The remaining 51 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 × 1 × 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 participants' age (p = 0.22), sex (p = 0.28) or years of education (p = 0.98) of participants undergoing scans in the two scanners. We also examined the potential impact on the brain scans due to the scanner change by analysing the average fold opening and sulcal depth of the baseline scans that were acquired by these two scanners. We found no significant difference (p = 0.72 for fold opening and p = 0.42 for sulcal depth) between the scans from the two scanners (see details of scanner contrast for each measure in Table S1, Figure S1 and Figure S2).

Image processing

Cortical sulci were extracted in three major steps. First, we removed non-brain tissue to produce images containing gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF) only, 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 SPM8 skull-cleanup tool (Ashburner, 2009). Second, images were segmented into GM, WM and CSF using histogram scale-space analysis and mathematical morphology (Mangin et al., 2004). Third, individual sulci were identified and extracted using the BrainVisa (BV) sulcal identification pipeline (version 4.5; Rivière et al., 2009). The medial surface of the cortical folds was calculated using a homotopic erosion technique, and a crevasse detector was used to reconstruct sulcal structure as the medial surface from the two opposing gyral banks that spanned from the most internal point of the sulcal fold to the convex hull of the cortex (Mangin et al., 2004). Statistical probabilistic anatomy map recognition method (Perrot et al., 2011) with both global registration and local registration was used to label sulci. It was proved to produce an improved accuracy of 70% in this study than the one generated by using