A slower rate of sulcal widening in the brains of the nondemented oldest old

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A B S T R A C T

The relationships between aging and brain morphology have been reported in many previous structural brain studies. However, the trajectories of successful brain aging in the extremely old remain underexplored. In the limited research on the oldest old, covering individuals aged 85 years and older, there are very few studies that have focused on the cortical morphology, especially cortical sulcal features. In this paper, we measured sulcal width and depth as well as cortical thickness from T1-weighted scans of 290 nondemented community-dwelling participants aged between 76 and 103 years. We divided the participants into young old (between 76 and 84; mean = 80.35; SD = 2.44; male/female = 76/88) and oldest old (between 85 and 103; mean = 91.74; SD = 5.11; male/female = 60/66) groups. The results showed that most of the examined sulci significantly widened with increased age and that the rates of sulcal widening were lower in the oldest old. The spatial pattern of the cortical thinning partly corresponded with that of sulcal widening. Compared to females, males had significantly wider sulci, especially in the oldest old. This study builds a foundation for future investigations of neurocognitive disorders and neurodegenerative diseases in the oldest old, including centenarians.

1. Introduction

There is increasing interest in the complex cerebral aging processes in elderly individuals, especially in the much less-studied oldest old. Variously defined as aged 80, 85 or 90 years and over (Liu et al., 2013; Mengel-From et al., 2013; Spaniolas et al., 2014; Willems et al., 2013), the nondemented oldest old represent a population of individuals with “successful brain aging” (Brodaty et al., 2016; Neltner et al., 2016), with possible resistance to neurodegeneration (Ebbing et al., 2010; Neltner et al., 2016; Silverman and Schmeidler, 2018). However, the available brain aging studies have focused mainly on relatively “young” elderly individuals with heterogenous patterns of brain changes (Fjell et al., 2014a; Fox and Schott, 2004; Hedman et al., 2012). The patterns of cortical atrophy in normal cognitive aging or associated with diseases found in the young old may not be applicable to individuals above the age of 85 (Boccardi et al., 2017; Jaul and Barron, 2017; Paolacci et al., 2017). Therefore, studying the cortical morphology in the oldest old will advance our understanding of the basis of cognitive reserve in extreme old age and provide a new perspective for use in future studies of normal and pathological aging in this cohort, which is an increasing population in our society.

There have been far more studies focused on the morphology of the young old than of the oldest old. Early longitudinal studies reported that the rates of global atrophy increased gradually with age from 0.2% per year between the ages of 30 to 50 years to 0.3–0.5% at 70–80 years old (Resnick et al., 2003; Scahill et al., 2003; Schott et al., 2003). Using voxel-based morphometry (VBM), several studies have found that the rate of atrophy or gray matter (GM) loss increases with age in some local regions (Driscoll et al., 2009; Jiang et al., 2014; Pini et al., 2016). In comparison to the large number of structural brain studies of the young old, only two studies have investigated structural alterations in the oldest old (Bennett et al., 2017; Yang et al., 2016). Bennett et al. (2017) re-
ported age-related differences in the white matter (WM) integrity of the oldest old, but their study did not focus on the changes between the oldest old and young old samples. Another study of a cohort aged between 71 and 103 years conducted by our own group reported a pattern of global and regional GM atrophy with increasing age, with the greatest age effects seen in the medial temporal lobe and parietal and occipital cortices. This pattern was further confirmed by directly comparing the ≥90 years old group to the 71–89 years old group (Yang et al., 2016).

A limitation of evaluating cortical changes using VBM and the cortical thickness is that these measures are not robust in cases of extreme old age and disease, as they are based on the contrast between GM and WM. The contrast between cerebral GM and WM decreases with age and disease (Cho et al., 1997; Steen et al., 1995). Sulcal-based analyses, on the other hand, do not depend on the diminished GM-WM boundary in the older brain. Sulcal measures in this study relied only on the contrast between the cerebrospinal fluid (CSF) and the cortex, which is usually clearly demarcated even in MRI scans of very old brains (Im et al., 2008; Kochunov et al., 2005). Because of this technical advantage, sulcal measures have been extensively employed in studies of brain aging (Kochunov et al., 2005; Liu et al., 2010; Madan, 2019; Shen et al., 2018) and neurodegenerative diseases (Amiez et al., 2018; Bertoux et al., 2019a; Liu et al., 2011). Furthermore, some studies have reported the sulcal width as a better measure compared to the cortical thickness, as it has demonstrated stronger correlations with cognitive performance (Bertoux et al., 2019a; Cai et al., 2017; Hamelin et al., 2015; Jouvent et al., 2011; Liu et al., 2011). Sex differences (Jin et al., 2018; Kochunov et al., 2005; Liu et al., 2010) and hemispherical asymmetry (Jeong and Xu, 2016; Jin et al., 2018; Leroy et al., 2015) in sulcal measures have also been reported. However, to date, there has been no structural brain study of the oldest old to take advantage of these sulcal measures.

The purpose of this study was to analyze the variation in the cortices of the young old and oldest old using the sulcal width and depth. Participants were from two community study cohorts and aged between 76 and 103 years. We validated our findings of the sulcal width and compared the results with those obtained using the cortical thickness. We also investigated sex differences and hemispherical asymmetry in the measured sulci.

2. Materials and methods

2.1. Participants

Participants were drawn from two community-based studies, the Sydney Memory and Aging Study (MAS) (Sachdev et al., 2010) and the Sydney Centenarian Study (SCS) (Sachdev et al., 2013). All participants received comprehensive assessments, with different neuropsychological batteries used for the MAS and SCS. Participants were excluded from the study if they had been diagnosed as having dementia. A total of 300 participants was recruited. We separated the participants into two age groups—the young old, aged 76–84 years (n = 166), and the oldest old, aged 85–103 years (n = 134), which allocated similar numbers of participants into the two groups (Slavin et al., 2013). One hundred and sixty-six participants in the young old group were drawn from the Fourth Wave of the MAS. Seventy-seven out of 134 participants in the oldest old group were from MAS Wave 4, and 57 were from the SCS. After the removal of the 10 scans that had failed key image processing steps, such as masking, segmentation or sulcus labeling, we ultimately included a sample size of 290 participants (young old, n = 164; oldest old, n = 126) in the study. There were no significant sex differences between the two groups. The demographic characteristics, including Mini-Mental Status Examination (MMSE) scores (Folstein, 1975), of the sample are presented in Table 1.

The study was approved by the human research ethics committee of the University of New South Wales.

2.2. Image acquisition and image processing

All scans were acquired using the same Philips 3T Achieva Quasar Dual scanner (Philips Medical Systems, Best, The Netherlands) located at the Prince of Wales Medical Research Institute, Sydney. The sequences used for the T1-weighted structural MRI scans were as follows: repetition time = 6.39 ms, echo time=2.9 ms, flip angle = 8°, matrix size = 256 × 256, field of view = 256 × 256 × 190, and slice thickness = 1 mm with no gap in between, yielding 1 × 1 × 1 mm³ isotropic voxels.

Cortical sulci were analyzed using three key steps. First, the non-brain tissue, such as the skull, was removed by warping a brain mask, which was obtained with SPMB (Ashburner, 2009), to produce images consisting only of GM, WM and CSF. Second, brain tissues were segmented into GM, WM and CSF through 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) (Perrot et al., 2011). The medial surface of the cortical folds was calculated by using a homotopic erosion technique, and the sulcal structure was reconstructed using a crevasse detector, as the medial surface from the two opposing gyral banks spanned from the most internal point of the sulcal fold to the convex hull of the cortex (Mangin et al., 2004). Individual sulci were labeled by global and local registration with statistical probabilistic anatomy map recognition (Perrot et al., 2011). This method has a proven improved accuracy of 70% in this study compared with the one generated by using artificial neural network-based pattern classifiers (accuracy of 63%) (Sun et al., 2007). The automlabelling results of all participants were visually inspected blind to age or sex, and the mislabeled sulci were manually corrected to ensure consistency and accuracy.

For each hemisphere, sulcal width and sulcal depth were determined for each of eight pairs of fissures, including intraparietal, central, suprarior frontal, superior temporal, subparietal, sylvian, posterior cingulate and anterior cingulate sulci (Fig. 1). These eight sulci were chosen because they were anatomically distinct and easy to identify in all individuals. Moreover, the eight pairs of sulci were located on both medial and lateral parts of the brain and were distributed on different cerebral lobes, thus providing comprehensive measures of the entire brain. The sulcal width, which is also known as the sulcal span (Liu et al., 2010) or fold opening (Reiner et al., 2012), was measured as the mean distance between the two walls of the pial surface defining the cortical sulci. The sulcal depth was defined as the maximal geodesic depth of the sulcal surface (Im et al., 2006). The mean sulcal depth was reported in this study because it is a robust measure and can be considered to represent the overall morphology of the whole sulcus.

We also computed the average regional cortical thickness using FreeSurfer 6.0.0 (http://surfer.nmr.mgh.harvard.edu/). Briefly, all images were processed with the automatic FreeSurfer “recon-all” pipeline to acquire volumetric information, whereas cortical thickness was determined as the average of the distance from a specific GM or WM boundary to the closest point on the GM or CSF boundary at each node on the image (Desikan et al., 2006; Reiner et al., 2012). FreeSurfer results were manually checked for segmentation and registration accuracy. To investigate the correlation between sulcal measures and cortical thickness, analysis was carried out within regions of interest (ROIs) that were adjacent to the eight selected sulci. The ROIs were defined based on the Desikan-Killiany atlas (DK, 34 regions per hemisphere) (Desikan et al., 2006). These cortical ROIs included the superior temporal, middle temporal, precentral, post-central, superior frontal, rostral-middle frontal, caudal-middle frontal, superior parietal, inferior parietal, pre-central, and para-central (see Fig. 1).

2.3. Statistical analysis

We tested the main effects of four variables, namely, age, sex, hemisphere, and years of education, on the sulcal features, including the sul-
Table 1
Sample characteristics.

|                          | Young old (76–84y) | Oldest old (85–103y) | T-test/Chi-square/Kruskal–Wallis H test | p   |
|--------------------------|---------------------|----------------------|----------------------------------------|-----|
| Number of subjects (male/female) | 164 (76/88)         | 126 (60/66)          | –                                      | –   |
| Age, years (mean±SD)     | 80.35±2.44          | 91.74±5.11           | –0.25 07                               | <0.001* |
| Female, %                | 53.6                | 52.3                 | 0.047                                  | 0.892^ |
| Education, years (mean±SD)| 12.19±3.62          | 11.22±3.59           | 2.272                                  | 0.024* |
| MMSE (mean±SD)           | 28.36±1.62          | 27.54±1.87           | 22.288                                 | <0.001* |

* Two-tailed t-test.
^ Chi-square test.
& Kruskal–Wallis H test.
\[ MMSE = \text{Mini Mental State Examination.}\]

Fig. 1. Panel I: sulcal structures used in calculating average sulcal width were superior frontal sulcus (A), central sulcus (B), intraparietal sulcus (C), sylvian fissure (D), superior temporal sulcus (E), subparietal sulcus (F), posterior cingulate sulcus (G) and anterior cingulate sulcus (H). Panel II: eleven cortical regions adjacent to the eight selected sulci were the rostral-middle frontal (I), superior frontal (J), caudal-middle frontal (K), pre-central (L), post-central (M), superior parietal (N), inferior parietal (O), superior temporal (P), middle temporal (Q), pre-cuneus (R) and para-central (S).

Cortical width and sulcal depth. For each of the eight sulci, age was treated as a continuous independent variable, and sex was entered into the analysis as a binary dummy variable. Cortical measures of the same structure on the two hemispheres were concatenated vertically. A dummy variable indicating hemisphere was included in the regression model to account for hemispheric effects. To control for individual brain size, total intracranial volume (ICV) was used as a covariate because brain size had a positive correlation with average sulcal width (Liu et al., 2011).

For each individual group, we used linear regression to analyze the relationship between sulcal measures and age for each of eight sulci after controlling for sex, years of education, hemisphere and ICV. To allow for meaningful comparisons between different within-group alteration rates regarding different sulci, the original regression coefficients were transformed to normalized values by dividing them by the baseline value of sulcal measures. The baseline value is the intercept of the regression line. For between-groups comparisons, slope differences were tested in two steps. First, a permutation test was used to evaluate the association between sulcal measures and age. Five thousand permutations were repeatedly conducted for each measured sulcus in both groups. Then, we analyzed differences in permutation results between groups for eight sulci separately. To examine the differences in sulcal features between groups, an independent sample t-test was used with the adjusted data for controlling for sex, years of education, hemisphere and ICV.

Independent sample t-tests were used to investigate the effects of categorical variables such as sex or hemisphere after controlling for the other factors in each group. Furthermore, the interactions between age and sex as well as between age and hemisphere were investigated for their relationships with sulcal measures. The interactive effects were investigated by testing the assumption of homogeneity of regression slopes in a repeated measure analysis of covariance (ANCOVA) model and using linear regression to investigate the difference in slope in individual groups. A statistical threshold of $p < 0.05$ was applied, and outcomes were corrected for multiple tests using the false discovery rate (FDR) (Benjamini and Hochberg, 1995). Kruskal–Wallis H test, a non-parametric method, was applied for MMSE score analysis, because MMSE scores were negatively skewed.

A general linear model (GLM) was used to investigate the relationship of cortical thickness change with age at the surface vertex by using FreeSurfer’s Qdec (http://surfer.nmr.mgh.harvard.edu/fswiki/FsTutorial/QdecGroupAnalysisV6.0). Age was used as a covariate, and sex was set as a fixed factor, while years of education was treated as a nuisance factor. Cortical thickness was not adjusted for each participant’s ICV (Westman et al., 2013). Statistical cortical thickness maps were constructed using $–\log_{10}(p)$ value. Statistical significance levels were corrected for multiple comparisons using FDR for both hemispheres. We also investigated the relationships between sulcal measures and the average cortical thickness of neighboring ROIs using Pearson correlations.

3. Results

3.1. Age effects on sulcal measures

In the young old, except for the sylvian fissure, the sulci significantly widened with increased age after FDR correction (Table 2). In the oldest old, while all measured sulci were found to significantly widen with increased age, two did not survive FDR correction (central sulcus, $p = 0.022$; anterior cingulate sulcus, $p = 0.035$) (Table 2). The estimated rates of sulcal changes differed across regions within groups compared with the regression coefficients for the normalized values (expressed as...
Table 2
Linear regression analysis in sulcal width and sulcal depth.

|                | Slope, mm/year (%) | Std.Error | T     | p     |
|----------------|---------------------|-----------|-------|-------|
| Young old      |                     |           |       |       |
| Sulcal         |                     |           |       |       |
| Sylvian        | 0.019               | 0.013     | 1.511 | 0.132 |
| Intraparietal  | 0.045               | 0.014     | 3.218 | 0.001 |
| Central        | 0.054               | 0.016     | 3.304 | 0.019 |
| Superior frontal | 0.069              | 0.018     | 4.299 | 0.001 |
| Superior temporal | 0.031              | 0.013     | 2.334 | 0.002 |
| Subparietal    | 0.034               | 0.015     | 2.289 | 0.023 |
| Posterior cingulate | 0.058             | 0.021     | 2.788 | 0.006 |
| Anterior cingulate | 0.045             | 0.017     | 2.712 | 0.007 |
| Sulcal depth   | 0.028               | 0.046     | 0.598 | 0.550 |
| Central        | −0.001              | 0.036     | −0.105| 0.988 |
| Superior frontal | −0.085             | 0.037     | −2.294| 0.022 |
| Superior temporal | −0.077             | 0.036     | −2.139| 0.033 |
| Subparietal    | −0.030              | 0.035     | −0.394| 0.681 |
| Posterior cingulate | 0.001             | 0.047     | 0.023 | 0.982 |
| Anterior cingulate | −0.020            | 0.024     | −0.831| 0.407 |
| Oldest old     |                     |           |       |       |
| Sulcal         | 0.028               | 0.007     | 4.117 | −0.001 |
| Intraparietal  | 0.036               | 0.009     | 3.990 | −0.001 |
| Central        | 0.020               | 0.009     | 2.310 | 0.022 |
| Superior frontal | 0.022              | 0.010     | 2.821 | 0.005 |
| Superior temporal | 0.027             | 0.008     | 3.390 | 0.001 |
| Subparietal    | 0.029               | 0.008     | 3.598 | −0.001 |
| Posterior cingulate | 0.038             | 0.012     | 3.266 | 0.001 |
| Anterior cingulate | 0.021             | 0.010     | 2.046 | 0.042 |

After adjusting for sex, hemisphere, years of education and intracranial volume (ICV) in linear regression models, examinations of age-related differences per year on sulcal width or sulcal depth were presented within the young old and the oldest old respectively.

a Slope, mm/year (the original regression coefficients were transformed to normalized values by dividing by the baseline value of sulcal measures: Slope/Baseline x 100%)

b FDR = false discovery rate, p = 0.05. The results survived FDR correction appeared in bold.

c Group difference in slopes

d Group difference in sulcal measures

After adjusting for sex, hemispheres, years of education and intracranial volume (ICV), sulcal measures differed in Table 3. Regarding sulcal width, the mean group differences ranged from 0.308 mm for the anterior cingulate sulcus to 0.509 mm for the posterior cingulate sulcus. Significant differences in sulcal depth between the two groups were found in the superior frontal sulcus, superior temporal sulcus and anterior cingulate sulcus, with shallower sulcal depths in the oldest old than in the young old (FDR corrected, Table 3).

Significant slope differences, namely, differences in regression coefficients between the two groups, represented the rate of change due to increased age. They were explored by examining the sulcal width and sulcal depth using permutation tests and t-tests (Table 3). Scatter plots with the estimated line of the best fit between the sulcal measures and age are shown in Fig. 2. The slopes of regression lines became flatter in the oldest old compared with those in the young old in several measured sulci. Except in the sylvian fissure, the rates of widening ranged from 0.031 mm/year (p = 0.020) in the superior temporal sulcus to
Fig. 2. After adjusting for sex, hemisphere, years of education and intracranial volume (ICV), scatterplots of linear regression of the sulcal width and sulcal depth of all individuals by young old and oldest old respectively (red line: young old, blue line: oldest old). $P_{\text{young}}$ and $P_{\text{oldest}}$ are the $P$-values of linear regression in the young old and in the oldest old respectively. * FDR = false discovery rate, $p = 0.05$. The results that survived FDR correction are in bold.

0.060 mm/year ($p = 0.001$) in the young old, and they decreased to the range of 0.020 mm/year ($p = 0.022$) in the central sulcus and to 0.038 mm/year ($p = 0.001$) in the posterior cingulate sulcus before FDR correction. Regarding the sulcal depth, we found a slowing of the relationship with age in the superior frontal sulcus before FDR correction, which became shallower at the rate of 0.085 mm/year ($p = 0.022$) in the young old; the rate then decreased to 0.045 mm/year ($p = 0.038$) in the oldest old.

3.2. Sex differences in sulcal measures

Sex differences in sulcal measures are shown in Table 4. Significant sex differences in sulcal widths were found in the intraparietal sulcus, central sulcus, and posterior cingulate sulcus in the young old after controlling for age, education, hemisphere and ICV (FDR corrected, Table 4). In addition to these three sulci, significant differences were found in the sylvian fissure, superior temporal sulcus, subparietal sulcus and anterior cingulate sulcus in the oldest old (FDR corrected, Table 4). These results suggested wider sulci in males than in females in both the young old and oldest old. Regarding sulcal width, a significant sex difference was only found in the superior frontal sulcus in oldest old (FDR corrected, Table 4). Interactions between sex and age were only observed in the young old, affecting the width of the sylvian fissure ($p = 0.015$), central sulcus ($p = 0.014$), subparietal sulcus ($p = 0.028$) and posterior cingulate sulcus ($p = 0.046$). A steeper age-sulcal width slope of sulci was ob-
Table 4
Sex difference and interactive effect (age × sex) in sulcal measures in young old and oldest old group separately.

| Sulcal Width | Young old | Interactive effect | Old old | Interactive effect |
|--------------|-----------|--------------------|--------|--------------------|
|              | Male      | Female             |        | Male               | Female             |        |
|              | Mean ± SE | p                  | F      | p                  | Mean ± SE          | p      |
| Male         | 2.332     | 2.334              | 0.002(0.062)| 0.971| 5.976              | 0.015 |
| Female       |           |                    |        |                   |                    |        |
| Central      | 2.361     | 2.147              | −0.214(0.069)| 0.002*| 2.897              | 0.090 |
| Superior frontal | 3.055 | 2.907              | −0.148(0.089)| 0.979| 3.708              | 0.055 |
| Superior temporal | 1.930 | 1.913              | −0.017(0.076)| 0.940| 2.572              | 0.110 |
| Subparietal  | 1.309     | 1.239              | −0.070(0.072)| 0.327| 4.899              | 0.028 |
| Posterior circulate | 2.511 | 2.244              | −0.267(0.101)| 0.009*| 4.008              | 0.046 |
| Anterior circulate | 1.977 | 1.851              | −0.126(0.082)| 0.124| 0.970              | 0.325 |

* Sulcal widths or sulcal depths in female minus those in the male in mm.

Table 5
Hemispheric differences and interactive effect (age × hemisphere) in sulcal width and sulcal depth in young old and oldest old separately. Hemispherical asymmetry of paired sulci was tested with hemisphere as binary dummy variable.

| Sulcal Depth | Young old | Interactive effect | Old old | Interactive effect |
|--------------|-----------|--------------------|--------|--------------------|
|              | Male      | Female             |        | Male               | Female             |        |
|              | Mean ± SE | p                  | F      | p                  | Mean ± SE          | p      |
| Male         | 14.273    | 14.322              | −0.400(0.227)| 0.079| 1.150              | 0.284 |
| Female       |           |                    |        |                   |                    |        |
| Central      | 14.447    | 14.244              | −0.203(0.176)| 0.251| 0.590              | 0.443 |
| Superior frontal | 11.885 | 11.840              | −0.045(0.181)| 0.805| 0.029              | 0.864 |
| Superior temporal | 14.053 | 14.110              | 0.057(0.175)| 0.746| 0.010              | 0.919 |
| Subparietal  | 7.868     | 7.722               | −0.147(0.170)| 0.389| 0.298              | 0.585 |
| Posterior circulate | 11.101 | 11.132              | 0.031(0.228)| 0.891| 2.330              | 0.128 |
| Anterior circulate | 8.762 | 8.720              | −0.041(0.119)| 0.729| 0.616              | 0.433 |

* Sulcal widths or sulcal depths in right sulcus minus those in the left in mm.

3.3. Hemispheric asymmetry on sulcal measures

Significant hemispheric asymmetries in sulcal depth were found in the intraparietal sulcus (p < 0.001 in both groups), superior temporal sulcus (p < 0.001 in both groups) and anterior circulate sulcus (p = 0.002 in the young old group) (FDR corrected, Table 5). The left superior temporal sulcus and anterior circulate sulcus were shallower than the corresponding sulci in the right hemisphere, while the intraparietal sulcus showed the opposite pattern. With regard to the sulcal width, significant hemispherical differences were found for the superior temporal sulcus (p = 0.001 in the young old group; p = 0.002 in the oldest old group) and subparietal sulcus (p = 0.001 in the oldest old group) (FDR corrected, Table 5), with wider sulcal widths in the right hemispheres. Interaction between age and hemisphere was only found in relation to the depth of the sylvian fissure in the oldest old (p = 0.012), but it became nonsignificant after FDR correction, suggesting that age differences in sulcal measures had a similar relationship in both hemispheres.

3.4. Association with cortical thickness

Surface-based analysis revealed age effects on the cortical thickness in the young old and oldest old groups (Fig. 3). In the young old, neg-
The color scale represents p-values after FDR correction for multiple testing. Blue–cyan indicates thinner cortex at higher age; red–yellow indicates the opposite. Sex differences maps were presented in young old (b) and in oldest old (c) respectively, after controlling for age and education. The color scale represents p-values without false discover rate (FDR) correction for visually demonstrate the widespread changes. Blue–cyan indicates thinner cortex at female; red–yellow indicates the opposite. Those maps were constructed using −log10(p value). Cortical maps were smoothed with full-width at half-maximum (FWHM). Gaussian kernel set at 10 mm.

Fig. 4. (a) Estimated group differences between young old and oldest old. The color scale represents p-values after FDR correction for multiple testing. Blue–cyan indicates thinner cortex at higher age; red–yellow indicates the opposite. Sex differences maps were presented in young old (b) and in oldest old (c) respectively, after controlling for sex and education. The color scale represents p-values without false discover rate (FDR) correction for visually demonstrate the widespread changes. Blue–cyan indicates thinner cortex at female; red–yellow indicates the opposite. Those maps were constructed using −log10(p value). Cortical maps were smoothed with full-width at half-maximum (FWHM). Gaussian kernel set at 10 mm.

Discussion

In the current study, we characterized age, sex, and hemispheric effects on brain sulcal measures in the young old (< 85 years old) and oldest old (≥85 years old) groups. Specifically, sulci were found to be wider with increased age in most measured sulci in both groups. The rates of sulcal widening and deepening were slower in the oldest old than in the young old. The widening of sulci was significantly associated with the thinning of their adjacent cortical regions, but sulcal measures were shown to be more sensitive to increased age than cortical thickness.

Our sample only included those who were willing to undergo an MRI scan, and the participants were considered to be physically health-
ier and slightly higher functioning when compared to the general oldest old population. Therefore, the inclusion of the oldest old means they are susceptible to this selection bias compared with a population-based sample. This needs to be taken account in the interpretation of the patterns observed.

4.1. Age-related differences

Our study showed that the sulcal width significantly increased with age in both the young old and the oldest old. The sulcal depth was less sensitive to age; however, there was a tendency toward shallower sulci with increased age. These findings were consistent with previous studies of sulcal morphology (Jin et al., 2018; Le Gruen et al., 2019; Liu et al., 2013b; Madan, 2019; Shen et al., 2018; Westman et al., 2013). This finding may be explained by the reduction of the cortical thickness, and the thinning of the cortex in turn may have resulted in the dilatation of the sulci (Im et al., 2008; Kochunov et al., 2008; Le Gruen et al., 2019; Liu et al., 2013b, 2013a). While we found significant correlations between the increase of the sulcal width and the decrease of the cortical thickness, the robustness of the two measures might differ. For example, we obtained a less significant relationship between the cortical thickness and age, but there was a more significant relationship between the sulcal width and age. This may be because the MRI contrast between GM and CSF remains more stable across the lifespan than does the GM/WM contrast, which may become increasingly more difficult to demarcate in the old brain (Im et al., 2008; Kochunov et al., 2005). Thus, sulcal measures could be good markers for studying the aging process in the old brain.

A noteworthy finding was the significant decrease in the rate of widening in the oldest old compared with the young old in seven sulci (intraparietal, central, superior frontal, superior temporal, subparietal, posterior cingulate and anterior cingulate sulci). Interestingly, finding of a previous study from our group was that there were turning points at around 75–80 years towards accelerating sulcal widening (Shen et al., 2018), but the oldest old who were over 85 occupied less than 10% of the total samples, while those who were over 90 occupied less than 1.5% of the total samples. It is possible that the result of Shen’s study could have been susceptible to outliers in extremely old age, owing to the limited sample sizes from 85 years onward. To date, no study has focused on investigating how changes occur in extremely old people. Both empirical and simulation modeling analyses have shown that age-related changes in sulcal morphology result from changes in brain gray and white matter (Im et al., 2008; Kochunov et al., 2008; Liu et al., 2013b; Tallinen et al., 2016, 2014). It has been reported that gray matter volume loss is a constant, linear function of age throughout adult life, whereas age-related atrophic degeneration was seen in frontal and anterior cingulate regions in recent studies (Fjell et al., 2014b; Storsve et al., 2014). Further, WM atrophy, which is an imaging marker of the progression of diseases including Alzheimer’s disease (AD) and stroke (Liu et al., 2017), was found to be delayed at advanced age (Yang et al., 2016). The findings of our study are in line with previous studies in that they showed a decreased atrophy rate in the cortex of the oldest old.

Moreover, the deceleration of sulcal widening in the oldest old may also support the hypothesis that the oldest old individuals still represent a population that is relatively resistant to degenerative brain processes, delaying or escaping senile diseases (Ebbing et al., 2010; Silverman and Schmeidler, 2018), because the relative “preservation” of the morphology could serve as the basis for understanding the mechanisms of exceptional longevity and/or cognitive maintenance at advanced ages (Yang et al., 2016). For example, we found a significant slowing rate of sulcal widening in the superior frontal sulcus and intraparietal sulcus, while the generally “preserved” part of the brain may relate to the reasons why near centenarians and centenarians have a stronger functional connectivity between the bilateral frontoparietal control network (Jiang et al., 2020). Moreover, a recent study reported that sulcal measures showed significant heritability estimates (Pizzagalli et al., 2020). This changes of sulcal morphology with age might be influenced by genetics. Sulcal morphology was reported as an efficient imaging marker of AD diagnosis, and related to its cognitive deficits (Bertoux et al., 2019b; Cai et al., 2017). Our finding could help to construct a standard to evaluate the efficacy of future disease modifying strategies for the oldest old individuals.

We only found the superior temporal sulcus to have significant correlations between the sulcal depth and local cortical thickness in the oldest old or in all individuals. Interestingly, this sulcus widened was at an almost constant rate throughout late life. These findings may be related to the specificity of this deep sulcus, which is often interrupted by buried transverse gyri with a high local fiber density (Le Gruen et al., 2018). Moreover, the sylvian fissure, which separates the temporal lobe from the frontal and parietal lobes, widened at a faster rate in the oldest old. It has been suggested that the temporal lobe is more vulnerable to the aging process compared to the frontal cortex, even for those who successfully age into extremely old age (Yang et al., 2016). The deformation of this sulcus was reported to be related to an alteration

Table 6

The correlation (R value) between sulcal measures and their neighboring cortical ROI’s average cortical thickness.

|                  | Sylvian 0.0152 | Intraparietal 0.1341 | Central 0.2061 | Superior frontal 0.2878 | Superior temporal 0.334v | Subparietal 0.372v | Posterior cingulate 0.390v | Anterior cingulate 0.350v |
|------------------|----------------|----------------------|----------------|-----------------------|------------------------|--------------------|--------------------------|------------------------|
| All samples      | −0.318 ± 0.05  | −0.423 ± 0.10       | −0.406 ± 0.15  | −0.168 ± 0.05         | −0.389 ± 0.05          | −0.372 ± 0.05      | −0.402 ± 0.05             | −0.183 ± 0.05           |
| Young old        | −0.263 ± 0.05  | −0.314 ± 0.10       | −0.276 ± 0.15  | −0.137 ± 0.05         | −0.317 ± 0.05          | −0.342 ± 0.05      | −0.372 ± 0.05             | −0.135 ± 0.05           |
| Oldest old       | −0.294 ± 0.05  | −0.462 ± 0.15       | −0.461 ± 0.15  | −0.191 ± 0.05         | −0.368 ± 0.05          | −0.321 ± 0.05      | −0.350 ± 0.05             | −0.226 ± 0.05           |
| Sulcal depth     | 0.050          | 0.073                | 0.016          | −0.022                | 0.122 ± 0.05           | −0.070             | 0.056                    | −0.005                 |
| Young old        | 0.043          | 0.078                | 0.022          | −0.021                | 0.040                  | 0.001             | 0.027                    | −0.038                 |
| Oldest old       | 0.028          | 0.045                | −0.037         | −0.032                | 0.153 ± 0.05           | −0.142 ± 0.05      | −0.079                   | 0.025                  |

* FDR = false discovery rate, p = 0.05. The results survived FDR correction appeared in bold.
* Correlations between sulcal measure in sylvian fissure and the average thickness in superior temporal cortex.
* Correlations between sulcal measure in intraparietal sulcus and the average thickness in superior parietal and inferior parietal cortices.
* Correlations between sulcal measure in central sulcus and the average thickness in pre-central and post-central cortices.
* Correlations between sulcal measure in superior frontal sulcus and the average thickness in rostral-middle frontal, superior frontal and caudal-middle frontal cortices.
* Correlations between sulcal measure in superior temporal sulcus and the average thickness in superior temporal and middle temporal cortices.
* Correlations between sulcal measure in subparietal sulcus and the average thickness in pre-cuneus cortex.
* Correlations between sulcal measure in posterior cingulate sulcus and the average thickness in para-cuneus and para-central cortices.
* Correlations between sulcal measure in anterior cingulate sulcus and the average thickness in superior frontal cortex.

1 p < 0.05 with Pearson correlation.

2 p < 0.01 with Pearson correlation.
of processing speed, which is a basic measure of processing efficiency (Liu et al., 2011). Because a decline in processing speed is a leading indicator of cognitive aging (Finkel et al., 2007), future studies to uncover the relationships between alterations of the sylvian fissure and cognitive performance may be interesting to investigate.

Regarding the sulcal width among the eight sulci, the subparietal sulcus and posterior cingulate sulcus, which are located between the precuneus and PCC, widened at a faster normalized rate compared to other sulci in both groups of our study. This area is important, as it is located in the crucial hubs of the default mode network (DMN) (Fransson and Marrelec, 2008; Greicius et al., 2003; Shen et al., 2018). The PCC, which is located in the posterior regions of the DMN, is particularly sensitive to aging (Andrews-Hanna et al., 2007; Mak et al., 2017). Previous studies have reported that aging was associated with less functional connectivity in the DMN (Damoiseaux et al., 2008; Liem et al., 2019; Tomasi and Volkow, 2012). We suggest, therefore, that this could be an interesting underlying mechanism for future studies to investigate in the relationship between atrophy in PCC and connectivity reductions in the DMN.

4.2. Sex differences

In the current study, we found that the mean sulcal widths were higher in men than in women for most of the measured sulci in both the young old and oldest old individuals. Sex differences have been reported for men and women between the ages between 64 and 70 years (Jin et al., 2018) and between 70 and 90 years (Liu et al., 2010) and it has been found that men have a significantly wider sulci than women. Sex differences in the sulcal width may be related to not only a larger brain structure in males than in females (Jäncke et al., 2015; Ritchie et al., 2018) but also a higher cortical thinning rate in males than in females (Curia et al., 2009; Raz et al., 2004). Moreover, sex differences have been reported to be promoted not only by differences in hormonal and physiological processes but also by different exposures to risk factors associated with neurodegeneration (Cherbuin et al., 2015). On the other hand, there was no significant interaction between age and sex in the sulcal width of any of the eight sulci that we examined, which suggested that both men and women experienced sulcal widening at the same rate, which is in line with previous findings (Liu et al., 2010).

4.3. Hemispheric asymmetry

Global hemispheric asymmetry has been previously reported, with the right hemisphere having a greater brain volume than the left hemisphere within the age range of 20–80 years (Raz et al., 2004). Interestingly, we observed that several sulci were wider or deeper in the right hemisphere than in the left hemisphere. Only the intraparietal sulcus showed the opposite pattern, which may have been caused by the structural asymmetries in the parietal cortex and lateralization of attention (Jeong and Xu, 2016; Jin et al., 2018). The hemispheric asymmetry observed in this sample is consistent with the literature (Le Guen et al., 2018; Liu et al., 2010; Shen et al., 2018). We found nonsignificant interactive effects between the hemisphere and age, suggesting that age differences in sulcal measures had a similar relationship in both hemispheres.

4.4. Limitation of our study

First, our conclusions on aging effects are based on cross-sectional data from two population-based studies. While age-related changes are best determined in longitudinal studies to avoid between-subject differences, there are practical difficulties in assessing individual variability in aging in the frail oldest old using a longitudinal design because of the high attrition rate seen in the very old. In addition, it is not known how sulcal feature changes are related to brain function alterations in the oldest old. We plan to relate sulcal morphology to neuropsychological test performance to determine the significance of these changes. Lastly, we examined only eight sulci. These eight sulci were chosen because they were anatomically distinct, easy to identify, and located on both medial and lateral parts of the brain and therefore, we believed that their measurements were robust. The other sulci detected by BrainVisa are worth further analysis in future work.

5. Conclusion

This study demonstrates hitherto unknown characteristics of the sulcal width and depth in an oldest old cohort aged 85–103 years and how they compare with those of a young old cohort aged 76–84 years. Differences in age, sex, and hemispheric effects on sulcal measures in both groups were also identified. These findings provide complementary information about brain alterations in the oldest old that benefit future populations and disease studies and provide key information about the characteristics of extreme aging in nonagenarians and centenarians.

Data and code availability statement

Due to the restriction of ethics, we are not able to make our data publicly available. However, our data can be obtained for research purposes through data request application to the governance committee (MED Cheba Data: ChebaData@unsw.edu.au).

Declaration of Competing Interest

The authors declare that they have no conflicts of interest.

Credit authorship contribution statement

Hui Tang: Methodology, Software, Formal analysis, Writing - original draft. Tao Liu: Conceptualization, Supervision, Methodology, Resources, Writing - review & editing, Funding acquisition. Hao Liu: Formal analysis, Writing - review & editing. Jiyang Jiang: Formal analysis, Writing - review & editing. Jian Cheng: Software, Writing - review & editing. Huijun Niu: Methodology, Writing - review & editing. Shuyu Li: Methodology, Writing - review & editing. Henry Brodsky: Resources, Writing - review & editing, Funding acquisition. Perminder Sachdev: Resources, Writing - review & editing, Funding acquisition. Wei Wen: Methodology, Resources, Writing - review & editing, Funding acquisition.

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