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The relationship between cortical sulcal variability and cognitive performance in the elderly

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ABSTRACT

The relationship between cognitive functions and brain structure has been of long-standing research interest. Most previous research has attempted to relate cognition to volumes of specific brain structures or thickness of cortical regions, with relatively few studies examining other features such as cortical surface anatomy. In this study, we examine the relationship between cortical sulcal features and cognitive function in a sample (N = 316) of community-dwelling subjects aged between 70 and 90 years (mean = 78.06 ± 4.75; male/female = 130/186) who had detailed neuropsychological assessments and brain MRI scans. Using automated methods on 3D T1-weighted brain scans, we computed global sulcal indices (g-SIs) of the whole brain and average sulcal spans of five prominent sulci. The g-SI, which reflects the complexity of sulcal folds across the cerebral hemispheres, showed a significant positive correlation with performance in most cognitive domains including attention/processing speed, memory, language and executive function. Regionally, a negative correlation was found between some cognitive functions and sulcal spans, i.e. poorer cognitive performance was associated with a wider sulcal span. Of the five cognitive domains examined, the performance of processing speed was found to be correlated with the spans of most sulci, with the strongest correlation being with the superior temporal sulcus. Memory did not show a significant correlation with any individual sulcal index, after correcting for age and sex. Of the five sulci measured, the left superior temporal sulcus showed the highest sensitivity, with significant correlations with performances in all cognitive domains except memory, after controlling for age, sex, years of education and brain size. The results suggest that regionally specific sulcal morphology is associated with cognitive function in elderly individuals.

Introduction

Attempts to relate brain structure to function have a long history, going back to the time of phrenology. Recent investigations have used advanced statistical techniques such as regional brain volumetrics or voxel-based morphometry (VBM) to examine the relationship. Positive correlations between brain structure and cognitive functions have been found, such as processing speed (Kochunov et al., 2010; Tisserand et al., 2000), executive function (Newman et al., 2007) and memory (Tisserand et al., 2000) in cognitively healthy adults. However, the studies have not always been consistent, and some surprising negative correlations have been reported, such as better memory being associated with smaller hippocampal volumes in healthy adults in one study (Van Petten, 2004). Furthermore, a review of the literature on structure–function correlations in aging suggested that "the magnitude of the observed associations is modest" (Raz and Rodrigue, 2006).

Quantification of the morphology of the fold on the cortical surface may be helpful in understanding the relationships between brain structure and function. The pattern of sulcal folds, the principal anatomical landmarks of the human cerebral cortex on the brain surface, exhibits its structural complexity (Welker, 1988) and reflects the underlying connectivity (Van Essen, 1997). In addition, it has been shown that the cortical folding patterns can predict cytoarchitecture beyond what was traditionally expected (Fischl et al., 2008). A review paper suggested that the fold geometry was a macroscopic probe for hidden architectural organization or developmental events (Mangin et al., 2010). Further, previous studies pointed out an advantage of

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sulcal model-based analysis using the contrast between gray matter (GM) and cerebrospinal fluid (CSF), which unlike the contrast between GM and white matter (WM), remains stable in older subjects (Im et al., 2008; Kochunov et al., 2005). In recent studies of sulcal-based analysis, it was found that folding patterns were modified in psychiatric syndromes and neurological disorders including Alzheimer's disease (Im et al., 2008; Mega et al., 1998), schizophrenia (Cachia et al., 2008) and bipolar disorder (Penttila et al., 2009). Furthermore, morphological difference of sulci had been found in certain professional groups, such as musicians (Li et al., 2009).

The first attempt to quantify the extent of the cortical folding relied on the gyrification index, namely, the ratio of the total pial cortical surface over the perimeter of the brain delineated on two-dimensional slices (Armstrong et al., 1995; Cachia et al., 2008; Luders et al., 2004; Zilles et al., 1988). Recently a new index of sulcal folds, called the global sulcal index (g-SI), has been computerized as a three-dimensional (3D) version of the gyrification index globally. The g-SI has shown a capacity for being a good biomarker in many studies (Mangin et al., 2010), for example, in detecting abnormalities in early-onset schizophrenia (Penttila et al., 2008) and intermediate-onset bipolar disorder (Penttila et al., 2008, 2009). The width of cortical sulci, called the sulcal span, has been proposed as another measure. Several studies have found that the width of cortical sulci expands linearly with aging from early adulthood to old age (Liu et al., 2010; Kochunov et al., 2005; Magnotta et al., 1999). Additionally, developmental abnormalities of cortical sulci in bipolar disorder were observed by examining the width of sulci (Coyle et al., 2006). A recent study also found that the average sulcal span in the frontal lobe was negatively associated with processing speed in 38 healthy elderly individuals (Kochunov et al., 2010).

In the present study, we investigate the relationship between cognitive function and global/regional sulcal morphometry based on the cortical surface of non-demented community-dwelling individuals in the age range of 70–90 years by examining the correlations between a range of neuropsychological domains (including attention/processing speed, memory, language, executive function and visuospatial ability) and sulcal features (including global sulcal index and five regional sulcal spans). To our knowledge, this is the first study to examine 3D cortical sulcal patterns in community-dwelling elderly with multiple cognitive domains. In a previous study, we reported that age was correlated with the sulcal pattern (Liu et al., 2010). In addition, age has been correlated with cognitive functions, and advancing age is generally accompanied by a decline in some cognitive functions (O'Sullivan et al., 2001). Therefore, we hypothesized that: i) poorer cognitive function will be associated with wider sulcal span and lower g-SI; ii) the sulcus–performance associations are only partially mediated by age, that is correlations between cognitive functions and sulcal features will be present after correcting for age effects; iii) processing speed, which shows the most consistent age-related decline (Salthouse, 1996; Tisserand et al., 2000), would have the most robust relationship with the global sulcal index and sulcal span; iv) there is regional specificity in the relationships, e.g. executive function with the superior frontal sulcus, language with the superior temporal sulcus, and visuospatial function with the intra-parietal sulcus; and v) we suspected that memory may not show a relationship with any of the sulci examined as the organs of memory are subcortical and are not reflected in these sulci.

Subjects and methods

Subjects

Participants were drawn from Wave 1 of the Sydney Memory and Aging Study (MAS), a prospective study examining the predictors of cognitive decline in an elderly, non-demented, community-dwelling sample. They were recruited randomly from the electoral rolls of two electorates of Eastern Sydney, Australia. Registration on the electoral roll is compulsory for Australian citizens. Participants were excluded from the study if they had been diagnosed as having any of the following: dementia, mental retardation, a psychotic disorder including schizophrenia or bipolar disorder, multiple sclerosis, motor neurone disease, active malignancy, and the inability to complete a basic assessment owing to a lack of proficiency in English (Sachdev et al., 2010). At study entry, participants were 1037 individuals aged 70–90 years, of whom 542 had an MRI scan. There were significant differences in sex, English-speaking background, education years, physical health and cognitive test scores between those who were willing to have a MRI scan and those who were not ($p<0.05$). The characteristics associated with those participants who were less likely to have an MRI scan included: being of female sex, non-English speaking background, having fewer years of education, poorer physical health and lower neuropsychological test scores. During image processing, 89 brain scans had to be excluded due to masking, segmentation or sulcus labelling errors (9% segmentation error and 7% sulcal extraction error). After the exclusion of participants of non-English speaking background, incomplete information of the neuropsychological tests (removing 137 subjects), 316 subjects with no significant sex difference on age ($T=1.07$, $p=0.28$), were entered into the study. Some demographic characteristics and mini-mental status examination (MMSE) score (Folstein et al., 1975) of the sample are presented in Table 1. It is noted that this was a healthy sample with a mean MMSE score of 28.57/30.

Image acquisition

Of the 316 subjects included in our study, 194 were scanned using a Philips 3T *Intera* Quasar scanner (Philips Medical Systems) located at the Prince of Wales Medical Research Institute, Sydney. The remaining subjects were scanned on a Philips 3T *Achieva* Quasar Dual scanner. The replacement of the scanner in 2007 was due to reasons beyond the control of the investigators. However, as subject recruitment was random, it was unlikely that any systematic sampling bias was introduced by the scanner change. Acquisition parameters for both scanners for T1-weighted structural MRI scans were identical; they were: 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 between; yielding $1\times1\times1$ mm^3 isotropic voxels. Participants scanned with the two different scanners were compared on social, demographic and imaging parameters, and there were no significant differences on sex, years of education, and age; GM, WM, CSF volumes and total intracranial cavity volume (ICV) of the whole brain were not significantly different between the scans of participants scanned by two different scanners after controlling for age, education and sex. We analyzed the scans of five healthy participants who were scanned on both scanners within two months, and no significant scanner differences were found in their sulcus morphometry (Liu et al., 2010). Furthermore, we did not find any significant scanner difference after examining the relationship between age and sulcal measures of the entire sample of these two scanners separately. Possible scanner effects were examined by using linear regression analysis of these five subjects. Nevertheless, a binary variable of "scanner" was included in the statistical analysis as an additional covariate to minimize the possible scanner effect.

Table 1
Demographic characteristics and MMSE score of the sample.

	Total N = 316	Male N = 130	Female N = 186	*t* value[a]	*p* value
Age (years)	77.85 (4.55)[b]	77.52 (4.37)	78.08 (4.66)	−1.07	0.28
Education (years)	11.79 (3.61)	12.67 (4.03)	11.18 (3.16)	3.68	<0.001
MMSE	28.57 (1.27)	28.41 (1.36)	28.68 (1.20)	−1.81	0.07

[a] Comparison between male and female by two-tailed *t* test.
[b] Mean (SD).

Image pre-processing

Cortical sulcus was extracted by the following three steps: First, we removed the non-brain tissue by warping a brain mask defined in the standard space back to the raw T1-weighted structural MRI scan. The brain mask was obtained from an automated skull stripping procedure based on SPM5's skull-cleanup tool (Ashburner and Friston, 2000). The brain images after non-brain removal consisted of GM, WM and CSF. Second, we segmented the brain tissues into GM, WM and CSF using a fuzzy-classifier-based, anatomical segmentation method (Mangin et al., 2004) to segment brain tissue into WM, GM and CSF, after applying a field inhomogeneity bias correction (Mangin, 2000). This procedure is not affected by the reduction of contrast between GM and WM often seen in the aging brain, as it mainly relies on the delineation of boundaries between gray matter and CSF (Jouvent et al., 2008; Mangin et al., 2004). Third, we used BrainVisa (BV) image processing pipeline (version 3.2.0; http://brainvisa.info/) to extract and identified the sulcus under our study. The medial surface of the cortical folds was then calculated using a homotopic erosion technique (Mangin et al., 1995). A crevasse detector was then used to reconstruct sulcal structures as the medial surfaces from the two opposing gyral banks that spanned from the most internal point of sulcal fold to the convex hull of the cortex (Mangin et al., 1995, 2004). Then, sulcus recognition (labeling) was performed using BV. The BV sulcal identification pipeline incorporates a congregation of 500 artificial neural network-based pattern classifiers. The neural networks were trained on a database of 26 expertly classified brain scans, resulting in a classification with a mean accuracy rate of 76% (Riviere et al., 2002).

Global sulcal index (g-SI)

The global sulcal index (g-SI) for each hemisphere was measured as the ratio between the total sulcal area and the outer cortex area (Cachia et al., 2008; Penttila et al., 2009). A cortex with extensive folding has a large g-SI, whereas a cortex with low degree of folding has a small g-SI (Fig. 1). In a previous study (Liu et al., 2010), we found that as a person ages, the g-SI becomes smaller. We computed the g-SI automatically with no manual intervention using BV.

Sulcal span (SS)

The average sulcal span for an individual sulcal structure was defined as an average 3D distance between opposing gyral banks along the normal projections to the medial sulcal mesh (Kochunov et al., 2008). Five primary and secondary fissures, including superior frontal sulcus in frontal lobe, intra-parietal sulcus in parietal lobe, superior temporal sulcus in temporal lobe, and interlobar sulci of central sulcus and Sylvian fissure, were selected for investigation from each hemisphere (Fig. 2). These sulci were chosen because: (1) they are present in all individuals; (2) they are large and relatively easy to identify for facilitating error detection; (3) they are located on different cerebral lobes; and (4) all five sulci are located on the lateral convex hemispheric surface, thus avoiding the potential artifact induced by the necessity to manually identify the AC–PC line. We carefully carried out visual inspection of the extraction and labeling for each individual scan in its 3D image and the mislabeled sulci were manually corrected. Approximately 10% (central sulcus) to 40% (superior frontal sulcus) sulci required manual correction in our study. The similar selection method has recently been applied to the study of cortical morphology in cerebral small vessel diseases (Jouvent et al., 2008) and a normal aging study (Kochunov et al., 2008).

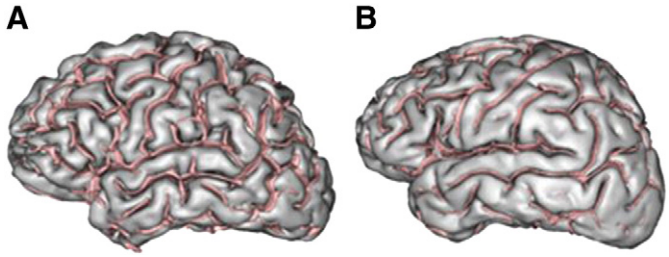

Fig. 1. The global sulcal index (g-SI) for each hemisphere is measured as the ratio between the total sulcal area and the outer cortex area. Two participants illustrate (A) a high and (B) a low overall g-SI.

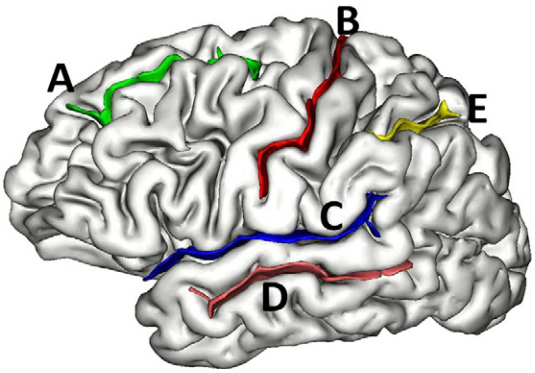

Fig. 2. Measurements were performed for the following sulcal structures: superior frontal sulcus (A) in the frontal lobe, interlobar sulci of central sulcus (B) and Sylvian fissure (C), superior temporal sulcus (D) in the temporal lobe and intra-parietal sulcus (E) in the parietal lobe.

In order to compare our sulcal measures with more classical ones, we computed the average regional cortical thickness using FreeSurfer 3.0.5 (http://surfer.nmr.mgh.harvard.edu/). Briefly, this process included automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures (Fischl et al., 2004), intensity normalization, tessellation of the gray/white matter boundary, automated correction of topology defects, surface deformation to form the gray/white matter boundary and gray/cerebrospinal fluid boundary, and parcellation of cerebral cortex (Desikan et al., 2006). Cortical thickness was calculated at each node, and average thickness was also calculated for each area of cortex parcellated (Fischl et al., 2004). The atlas used, detailed in Desikan et al. (2006), included 34 cortical regions of interests in each hemisphere.

Neuropsychological tests

A comprehensive neuropsychological test battery was administered by trained research psychologists. Twelve tests were administered that measured five cognitive domains (Table 2): attention/

Table 2
Cognitive domains and neuropsychological tests used in the current study.

Cognitive domain	Neuropsychological test	N	Mean	SD
Processing speed	Digit symbol coding	316	50.13	12.17
	Trail making test A	316	44.7	15.53
Memory	Logical memory (story A, delayed recall)	311	9.53	4.1
	Rey Auditory Verbal Learning Test Total learning (sum of trials 15)	316	41.69	9.27
	Rey Auditory Verbal Learning Test Short-term delayed recall (trial 6)	315	8.25	3.26
	Rey Auditory Verbal Learning Test Long-term delayed recall (trial 7)	315	7.83	3.49
	Benton Visual Retention Test	316	11.99	1.76
Language	Boston Naming Test — 30 items	316	25.21	3.48
	Semantic fluency (animals)	316	16.18	4.47
Visuospatial function	Block design	316	22.39	7.83
Executive function	Controlled Oral Word Association Test (FAS)	316	37.9	12.09
	Trail Making Test B	316	114.4	51.75

processing speed, memory, language, visuospatial and executive function. Digit Symbol-Coding task (Wechsler, 1997a) and Trail Making Test part A (TMT A) (Strauss et al., 2006) were used to assess attention/processing speed. Assessment of memory included: Logical Memory story A (Wechsler, 1997b), three measures from the Rey Auditory Verbal Learning Test (RAVLT) (Rey, 1964) — total learning (sum of trials 1–5), short-term delayed recall (trial 6) and long-term delayed recall (trial 7), and the Benton Visual Retention Test — multiple choice version (BVRT) (Benton and Spreen, 1996). Semantic fluency (Animals) (Spreen and Benton, 1969) and the 30 item Boston Naming Test (BNT) (Kaplan, 2001) were included as measures of language. Executive function was assessed using the Controlled Oral Word Association Task (COWAT) (Benton, 1967) and Trail Making Test part B (TMT B) (Strauss et al., 2006). Visuospatial skills were assessed using the Block Design task (Wechsler, 1981).

Statistical analysis

Raw neuropsychological assessment scores were transformed to z scores based on sample means and standard deviations, and domain composite scores were calculated by averaging z scores of the component tests. The signs of the Z scores of TMTA and TMTB were reversed, so that for all composites of cognitive domains, more positive scores represented better performances. Significant inverse relationships were observed between age and performances on all neuropsychological measures therefore we controlled the age effect in this study. In all the analyses, total intracranial cavity volume (ICV) was also used as a covariate to control for individual brain size because the brain size had a significant positive correlation with g-SI ($r=0.20$, $p<0.001$) and average sulcal span ($r=0.13$, $p<0.001$).

The effects of sulcal features including g-SI and sulcal span (SS) factors were tested on the five cognitive domain scores using multivariate analysis of covariance (MANCOVA), controlling for demographic effects, i.e. age, sex and years of education. Sex was treated as a fixed factor of 2 levels (male and female), hemisphere as a within-subjects factor of 2 levels (left and right), region mark as a within-subjects factor of 5 levels (five different sulci) and age and years of education as continuous covariates in separate general linear models investigating the relationship between sulcal morphology and cognitive function. An interactive effect between hemisphere, sex and region was subsequently tested. If the interactive effect was found to be significant, we then separated the model by the simple effects in the subsequent correlation analyses. Partial correlation and linear regression were then used to investigate the relationship between cognitive domains and sulcal feature after controlling for the other factors.

We also examined the relationship between cortical thickness and cognitive scores using partial correlation after correcting for age, sex, years of education and brain size. The false discovery rate (FDR) (Benjamini and Hochberg, 1995) was used for multiple comparison corrections.

Results

We found that g-SI significantly decreased with advancing age ($F(1, 622)=5.822$, $p=0.016$) and the widths of all five sulcal spans increased significantly with age (Wilks's Lambda $=0.830$, $F(6, 620)=21.134$, $p<0.001$,), after controlling for sex, ICV, scanner and hemisphere. Therefore, to investigate the correlations between cognitive function and sulcal features, we treated age as a covariate on the change of sulcal morphology.

Globally, partial correlation analysis showed that there were positive correlations between g-SI and the performances in most cognitive domains, namely processing speed ($r=0.104$, $p=0.009$), memory($r=0.109$, $p=0.006$), language($r=0.118$, $p=0.003$) and executive function ($r=0.126$, $p=0.002$), but not visuospatial function ($r=0.062$, $p=0.122$), after controlling for age, sex, education and ICV. The finding indicated that higher complexity of sulcal folds reflected better cognitive function.

Regionally, the results of age-uncorrected and age-corrected correlation analyses between the five cognitive domains and the five sulcal spans for the two hemispheres are presented in Table 3. Briefly, a large number of correlations between sulcal spans and performances in cognitive domains were negative, meaning that wider sulcal spans reflected poorer cognitive performances. Of the five cognitive domains, processing speed performances most strongly correlated with sulcal spans. Processing speed score was negatively correlated with sulcal span in bilateral Sylvian fissures (left: $r=-0.154$, $p=0.007$ and right: $r=-0.123$, $p=0.031$), bilateral intraparietal sulci (left: $r=-0.148$, $p=0.009$ and right: $r=-0.136$, $p=0.016$), bilateral superior frontal sulci (left: $r=-0.139$, $p=0.014$ and right: $r=-0.156$, $p=0.006$) and bilateral superior temporal sulci (left: $r=-0.173$, $p=0.002$ and right: $r=-0.192$, $p=0.001$), after age correction. With respect to memory, before controlling for age effects, memory scores were negatively correlated with spans of all sulci except the central sulcus, but these correlations were not significant after age correction. Although visuospatial ability did not significantly correlate with g-SI, it had a negative correlations with sulcal span, especially with the right superior frontal sulcus ($r=-0.168$, $p=0.003$) and bilateral superior temporal sulci (left: $r=-0.138$, $p=0.015$ and right: $r=-0.123$, $p=0.031$), after controlling for age. Negative correlations between language performance and sulcal span were detected widely in both hemispheres; however, after controlling for age, most correlations with right hemispheric sulci became non-significant. Age-corrected correlations with language were significant with the left intraparietal sulcus ($r=-0.128$, $p=0.023$), left superior temporal sulcus ($r=-0.164$, $p=0.004$) and bilateral superior frontal sulci (left: $r=-0.112$, $p=0.049$ and right: $r=-0.116$, $p=0.041$). The performance in executive function was negatively correlated with sulcal span in all sulci except central, but after correcting for age effects, only the left superior temporal remained a significant correlation ($r=-0.154$, $p=0.006$). We used FDR to calculate the FDR thresholds for p values, and 0.031, 0.004 and 0.003 were used for the multiple comparisons for processing speed and language and spatial, respectively in the partial correlation analysis between SS and cognitive domains after controlling for age, sex, education and brain size.

The sulcal feature related interactive effects of g-SI/SS × sex and g-SI/SS × hemisphere on cognitive domains were investigated in 14 separate models using MANCOVA, and the main fixed factors of sex, age, ICV, year of education, and hemisphere were controlled for. Our results showed no significant cognitive function related interactive effects of g-SI × sex (Wilks's Lambda $=0.993$, $F(5, 619)=0.860$, $p=0.508$), g-SI × hemisphere (Wilks's Lambda $=1.00$, $F(5, 619)=0.025$, $p=1.000$), SS × sex or SS × hemisphere, suggesting no sex-differences or hemispheric asymmetry on g-SI or SS in relation to cognitive function. We therefore combined the data of male and female subjects, controlling for sex as a fixed factor in the analysis. When the sulcal feature related interactive effects of SS × region on performances in cognitive domains were tested, we found significant regional interactive effects of region × SS on performances in the domains of processing speed ($F(5, 3774)=2.943$, $p=0.012$) and executive function ($F(5, 3774)=3.067$, $p=0.009$), which suggested that the cognitive functions were associated with sulcal span changes differently in different regions (Table 3). Furthermore, using MANCOVA, we found that central sulcus had no significant relationship with performances in any of the five cognitive functions (left: Wilks's Lambda $=0.985$, $F(5, 304)=0.901$, $p=0.480$ and right: Wilks's Lambda $=0.969$, $F(5, 304)=1.925$, $p=0.090$), while the left superior temporal sulcus showed the highest sensitivity, being negatively associated with performances in all five cognitive domains (Wilks's Lambda $=0.957$, $F(5, 304)=3.459$, $p=0.009$), after controlling for the effects of age, sex and brain size. Linear regression analysis showed

Table 3
Age-uncorrected (UNCORR.) and age-corrected (AGE-COR.) partial correlation between regional the right (R)/left (L) sulcal span and cognitive function scores for the elderly subjects (n = 316), after controlling for sex, education and brain size.

Sulcal span		Processing speed		Memory		Language		Spatial		Executive	
		UNCORR.	AGE-COR.	UNCORR.	AGE-COR.	UNCORR.	AGE-COR.	UNCORR.	AGE-COR.	UNCORR.	AGE-COR.
Sylvian fissure	L	−0.226*	−0.154*	−0.132*	−0.053	−0.145*	−0.087	−0.167*	−0.097	−0.159*	−0.104
	R	−0.191*	−0.123*	−0.128*	−0.055	−0.102	−0.046	−0.154*	−0.089	−0.099	−0.046
Intraparietal	L	−0.233*	−0.148*	−0.158*	−0.067	−0.193*	−0.128**	−0.167*	−0.085	−0.127*	−0.061
	R	−0.234*	−0.136*	−0.161*	−0.057	−0.178*	−0.103	−0.212*	−0.122**	−0.044	0.041
Central	L	−0.049	0.046	−0.055	0.036	−0.091	−0.025	−0.07	0.012	0.011	0.081
	R	−0.087	−0.007	−0.033	0.051	−0.099	−0.041	−0.147*	−0.08	0.03	0.094
Superior frontal	L	−0.233*	−0.139*	−0.146*	−0.044	−0.184*	−0.112**	−0.168*	−0.077	−0.063	0.016
	R	−0.240*	−0.156*	−0.114**	−0.019	−0.181*	−0.116**	−0.242*	−0.168*	−0.165*	−0.102
Superior temporal	L	−0.235*	−0.173*	−0.147*	−0.079	−0.212*	−0.164*	−0.197*	−0.138**	−0.200*	−0.154**
	R	−0.249*	−0.192*	−0.130*	−0.066	−0.128**	−0.08	−0.178*	−0.123**	−0.143*	−0.098

* Statistically significant at p<FDR threshold.
** Statistically significant at p<0.05.

that the left superior temporal sulcus had a significant negative relationship with performances in four cognitive domains, i.e. processing speed (β = −0.284, t = −3.023, p = 0.003), language (β = −0.286, t = −2.916 p = 0.004), visuospatial (β = −0.213, t = −2.406, p = 0.017) and executive function (β = −0.258, t = −2.738, p = −0.007) (Fig. 3), after controlling for age, sex and education.

Similar to the correlations between sulcal span and cognitive performances, after controlling for age, sex, education and ICV in partial correlation analysis, we have also found some significant correlations between cortical thickness and cognitive scores. The cortical thickness of temporal region and front region showed significant correlations with many cognitive performances, including, left superior temporal gyrus and visuospatial (r = 0.132, p = 0.030); left middle temporal gyrus and visuospatial (r = 0.130, p = 0.033), left superior frontal gyrus with memory (r = 0.142, p = 0.019), left middle frontal gyrus with memory (r = 0.191, p = 0.002), left superior temporal gyrus with memory (r = 0.159, p = 0.009) and left middle temporal gyrus with memory (r = 0.136, p = 0.025). Correlations between language performance and cortical thickness were also detected in the left superior parietal cortex (r = 0.146, p = 0.016), left interior parietal cortex (r = 0.182, p = 0.003) and the left middle temporal gyrus (r = 0.144, p = 0.018). However, none of the above correlations survived FDR corrections.

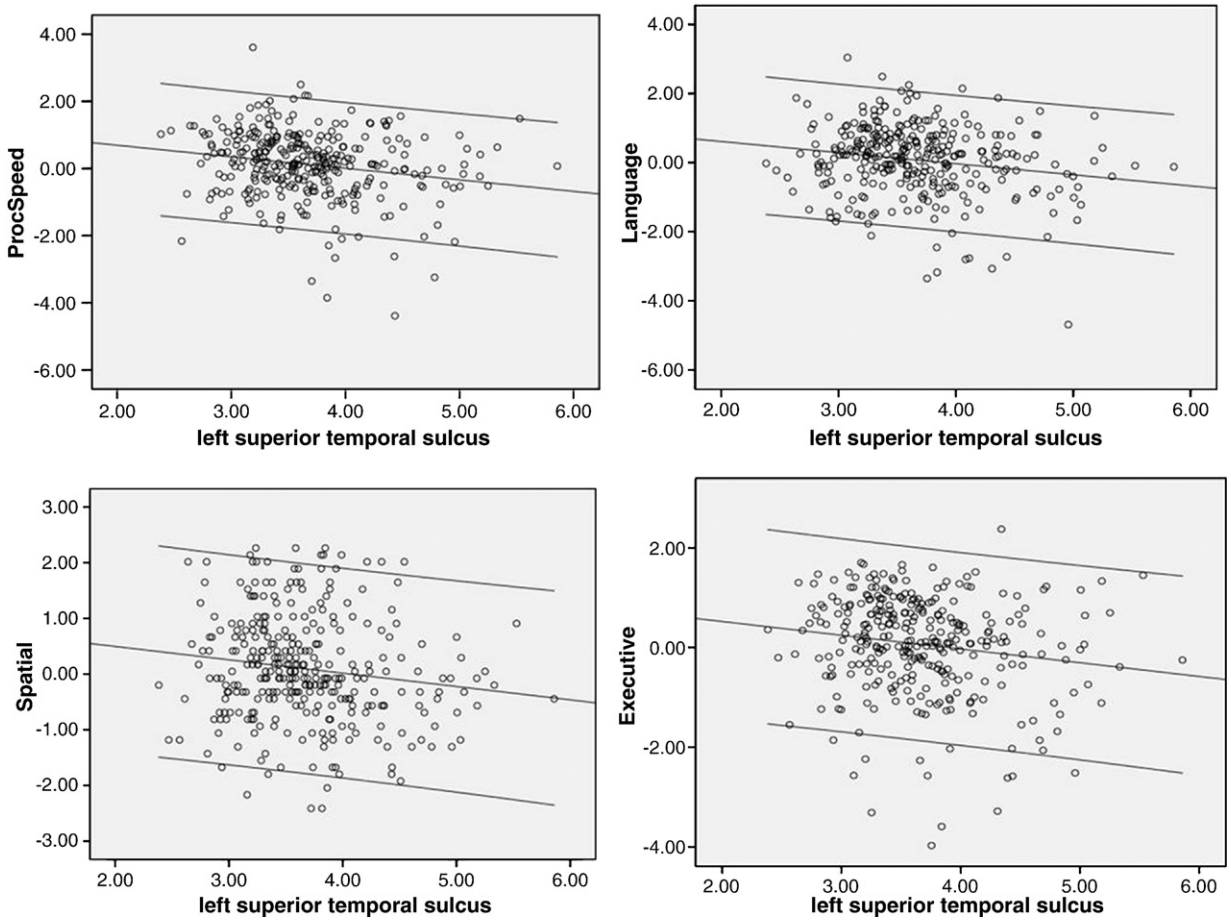

Fig. 3. Scatter plots and regression lines for the left superior temporal sulcus (mm) vs. z-scores of processing speed (β = −0.284, t = −3.023, p = 0.003), language (β = −0.286, t = −2.916 p = 0.004), visuospatial (β = −0.213, t = −2.406, p = 0.007) and executive functions (β = −0.258, t = −2.738, p = 0.007). The z-scores have been the correction for age, sex and years of education.

Discussion

The aim of the current study was to examine the relationship between cognitive function and the fold geometry of a set of sulcal regions in an elderly population. It has previously been shown that advancing age leads to an increase in the widths of sulci and a decrease in g-SI (Kochunov et al., 2005; Liu et al., 2010), as well as a decline in neuropsychological performances (O'Sullivan et al., 2001). Age-related cognitive changes in the elderly are possibly related to age-related brain structure changes (Raz and Rodrigue, 2006). Therefore our findings of the correlations between cognitive functions and cortical sulcal variability were consistent with our predictions.

We found that some correlations between cognitive domains and sulcus spans were not significant after controlling for age, especially for memory and executive domains. The sulcus-related correlations of some cognitive domains, such as processing speed, were significant after age correction. The impact of controlling for age reflects the fact that age-related structural change can partially mediate the correlations between cognition and brain structure (Raz and Rodrigue, 2006). A recent study reported that the significant correlations between cognitive domains and cortical thickness became weaker or became non-significant in most regions after correcting for age (Chee et al., 2009). Conversely, the detection of significant sulcus-related correlations of certain cognitive domains such as processing speed after age correction indicated that regionally specific changes in sulcal morphology are associated with specific cognitive function.

Cognitive functions and g-SI

The mechanism involved in the plasticity of the nervous system is thought to support cognition (Burke and Barnes, 2006). It has also been suggested that an increase in the number of neurons results in surface expansion (Penttilä et al., 2009). As the definition suggests, g-SI describes the structural properties of the folding surface. Therefore, the mechanism might explain our observations of the association between g-SI measure and cognitive performance. The cortical folding process that ultimately produces the mature sulco-gyral pattern is mediated by forces that stem from GM thickness and WM connectivity, which present associations with cognition. Moreover, g-SI also reflects the cortex gyrification. Mangin et al. (2010) suggested that deviations of cortex gyrification were related to clinical symptoms and cognitive deficits. In our study, lower g-SI was associated with worse cognitive performance. A recent study documented that the gyrification index of mild Alzheimer's disease patients is significantly lower than control subjects (King et al., 2010). Our subjects were elderly individuals who did not have a diagnosis of dementia. However, a significant proportion had memory complaints or mild decrements in cognitive performance, and the presence of subclinical neurodegenerative or vascular pathology was quite likely. It is possible that such pathology contributed to both sulcal width and cognitive deficits and may underpin some of this relationship. Our choice of an older population for such a study was due to the fact that older individuals show greater variability in sulcal width and the relationship with cognitive function is more likely to be apparent. While we have not examined a younger population on this measure, we suspect that the same relationship is not likely to be present in younger individuals. In summary, we suggest that in elderly individuals, the more complex the sulcal folds globally in the brain, the better the cognitive function of the individual.

Cognitive functions and sulcal span (SS)

Processing speed (PS)

As a basic measure of processing efficiency, processing speed is likely to be influenced by the integrity of sensory and pattern recognition processes which are dependent upon the integrity of the brain (Peers et al., 2005; Salthouse, 1996; Tisserand et al., 2000), including both grey and white matter (Dow et al., 2004; Turken et al., 2008; Wen and Sachdev, 2004). In addition, decline in processing speed is prominent in the elderly, and becomes even more prominent during the time course of neurodegenerative dementias (Hedden and Gabrieli, 2004, 2005; Wen et al., 2011). Therefore, a good correspondence between PS and sulcal span (SS) was expected in the elderly. In our study, after controlling for age, years of education and brain volume effects, PS appeared to have the most prominent correlation with SS among all the cognitive domains. The sulcal deformation related with processing speed was detected in the bilateral Sylvian fissures, bilateral intraparietal sulci, bilateral superior temporal sulci and bilateral superior frontal sulci, but not with the central sulci. The correlation with the Sylvian fissure may reflect the functions of temporoparietal junction cortex which is at the posterior end of the Sylvian fissure. Further, the temporoparietal junction lesions may lead to the decrease of speed of stimulus identification which is reflected in the speed of processing (Peers et al., 2005). The deformation of superior temporal sulcus (STS) may reflect morphologic change of superior temporal gyrus, which includes primary auditory cortex and Wernicke's area, an important region for the processing of speech (Cuenod et al., 1995). PS did not correlate with the central sulcus, which separates the frontal from the parietal lobe; while PS had negative correlations with superior frontal sulcus and intraparietal sulcus. Decreased activation of the frontal lobe has been observed in slower and less accurate groups relative to controls in tasks designed to assess reaction time and speed of processing (Rypma et al., 2007). In addition, decreased activation of the frontal and parietal lobes was detected in groups with processing speed deficits in a recent fMRI study (Genova et al., 2009). The correlation with the frontal sulcus was also consistent with prior studies which found a significant correlation between sulcal span in frontal lobe and PS (Kochunov et al., 2010). Processing speed had also been considered as an effective tool for clinical detection of neurological disorders (Keefe et al., 2006). Therefore, the extensive and strong correlations between cortical surface and processing speed may indicate the value of sulcal geometry in clinical diagnosis.

Memory

When age-related variance was taken into account, the sulcal spans did not relate to memory performance. There are a number of possible explanations for this: i) memory function is largely dependent upon the integrity of subcortical structures such as the hippocampus (Golomb et al., 1994), parahippocampal gyrus (Jack et al., 1992), maxillary bodies, etc., the size of which is not reflected in the sulcal geometry measured in this study. ii) The memory functions might be affected mainly by substantial structure losses, leading to a threshold effect (De Leon et al., 1997), iii) while the dorsolateral prefrontal cortex and the anterolateral temporo-polar regions are important for retrieval of memory (Markowitsch, 1995), there may be significant redundancy in the system for this not to manifest in a relationship between memory function and the widths of frontal sulci or the Sylvian fissures, over and above what is accounted for by age.

Language

A review by Vigneau et al. (2006) indicated that the left inferior parietal regions, left inferior frontal gyrus, left middle frontal gyrus, left superior temporal gyrus and the left supramarginal gyrus were organized into two neural components dedicated to speech, sound perception, and production: a fronto-temporal auditory–motor network and a fronto-parietal loop for phonological working memory. In addition, superior temporal gyrus and inferior frontal gyrus played an important role in semantic, phonological processing and sentence comprehension. Our observations of associations between language performance and sulcal span in the left intraparietal sulcus (above the horizontal portion of the inferior parietal regions), left superior frontal

sulcus (above the horizontal portion of inferior frontal gyrus and middle frontal gyrus) and left superior temporal sulcus (below the horizontal portion of superior temporal gyrus) are consistent with the above model.

Visuospatial function

Visuospatial functions have been consistently associated with predominantly right hemispheric regions (Marshall and Fink, 2001). The parietal cortex has been shown to code for the location of visual stimuli (Sereno and Huang, 2006), and lateral intraparietal cortex has been found to be involved in the control of spatial attention (Beauchamp et al., 2001; Hagler et al., 2007). Hagler and Sereno (2006) found that the superior frontal cortex played an important role in the attention to objects in a particular spatial location. Therefore, good performance on visuospatial function seems to be indicative of appropriate functioning of the lateral intraparietal area and frontal cortex, especially in the right hemisphere. These expectations are consistent with our finding that there is a significant correlation between visuospatial ability and right superior frontal sulcus, and the right intraparietal sulcus.

Executive function

Executive function has generally been referred to as a "higher-level" cognitive function and is thought to be attributed to the anterior brain regions such as the frontal lobes (Reitan and Wolfson, 1994). We found significant correlations between superior frontal sulcus and executive task, but the correlation became non-significant after correcting for age effects. This lack of an independent relationship may be due to redundancy in the brain systems underlying executive function, such that width of one frontal sulcus may not relate to function is this domain. A recent review study also found inconsistent support for the historical association between executive functions and the frontal lobes and they discussed the lack of direct association between damage to the prefrontal cortex and poor performance on executive task (Alvarez and Emory, 2006). After correcting for age, we found that only the superior temporal sulcus remained significantly associated with executive tasks. This may, we suggest, be related to the verbal aspects of the executive tasks.

Superior temporal sulcus (STS) and cognitive functions

Our most robust findings associated with cognitive function were in relation to the superior temporal sulcus. The STS is the main sulcal landmark of the external temporal cortex, and the deformation of STS might reflect a morphologic change of the superior temporal gyrus, which includes the primary auditory cortex and Wernicke's area, and is an important region for the processing of speech (Cuenod et al., 1995). STS as a landmark is also inside the paralimbic belt and was found to be similarly affected by the age-related pathologic process (Mega et al., 1998). Furthermore, the STS extends along the entire lateral ventricle and crosses the superior temporal sulcus multisensory area, which is important for integrating auditory and visual information (Zheng et al., 2010). In summary, because of the breadth of the area that involves the STS, the widespread correlates of cognitive function with STS were not unexpected. Our data suggest that the sulcal width of the STS might be a useful biomarker of cognitive dysfunction if one sulcal size is to be selected for measurement.

Comparison with cortical thickness analysis

In our study, both cortical thickness and sulcal span were found to correlate with cognitive performances in the domains of language, visuospatial and executive functions in similar regions before FDR correction. However, after using FDR for multiple comparison correction, no significant correlations between cortical thickness and cognitive functions were found. This finding was consistent with the results of the study by Chee et al. (2009). On the other hand, we observed significant associations between processing speed and both g-SI and local SS in the cortical surface analysis even after FDR correction. The cortical surface area and cortical thickness are essentially unrelated genetically and they are two distinct sources of genetic influences (Panizzon et al., 2009).Therefore, there is the possibility that the sensitivity of the correlations between cognitive functions and cortical thickness is different from that between cognitive function and sulcal span. The link between processing speed and sulcal span is also consistent with the findings in Kochunov et al. (2010).

Limitations of the study

Firstly, this is a cross-sectional examination and does not permit a causal inference between structural change and cognitive function. Because age-related cognitive deficits are best determined in a longitudinal study, in the next work, we will use our wave 2 scans which were taken two years after wave 1 scans to carry out a longitudinal study. Second, as our sample was aged 70–90 years, our findings are restricted to the elderly. Third, since our sample only included those who were willing to undergo a MRI scan, the participants were probably physically healthier and slightly higher functioning than those who did not agree to undergo a scan. Nevertheless, we consider it unlikely that this would have influenced the salient findings of our study.

Conclusion

We report widespread correlations of cortical surface anatomy, especially in the frontal and temporal regions, with cognition in non-demented elderly individuals. To our knowledge, this is the first study to examine 3D cortical sulcal patterns in healthy elderly with multiple cognitive domains. The salient findings are that processing speed has a broad and dispersed range of correlations with the cortical surface, with the strongest correlation being with the superior temporal sulcus, while no significant relationship between sulcal morphology and memory was detected. Globally, the complexity of sulcal folds is associated with better cognitive function in older individuals, after age-related changes have been accounted for. Cortical surface anatomy may serve as potential biomarker of cognitive function in the elderly and is worthy of further study.

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