Original Article

# Age- and sex-related differences in cortical morphology and their relationships with cognitive performance in healthy middle-aged and older adults

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**Background:** The impacts of age and sex on brain structures related to cognitive function may be important for understanding the role of aging in Alzheimer disease for both sexes. We intended to investigate the age and sex differences of cortical morphology in middle-aged and older adults and their relationships with the decline of cognitive function.

**Methods:** In this cross-sectional study, we examined the cortical morphology in 204 healthy middle-aged and older adult participants aged 45 to 89 years using structural magnetic resonance imaging (sMRI) data from the Dallas Lifespan Brain Study data set. Brain cortical thickness, surface complexity, and gyrification index were analyzed through a completely automated surface-based morphometric analysis using the CAT12 toolbox. Furthermore, we explored the correlation between cortical morphology differences and test scores for processing speed and working memory.

**Results:** There were no significant interactions of age and sex with cortical thickness, fractal dimension, or gyrification index. Rather, we found that both males and females showed age-related decreases in cortical thickness, fractal dimension, and gyrification index. There were significant sex differences in the fractal dimension in middle-aged participants and the gyrification index in older adult participants. In addition, there were significant positive correlations between the cortical thickness of the right superior frontal gyrus and Wechsler Adult Intelligence Scale (WAIS)-III Letter-Number Sequencing test scores in males (r=0.394; P<0.001; 95% CI for r values 0.216–0.577) and females (r=0.344; P<0.001; 95% CI for r values 0.197–0.491), respectively. Furthermore, a significant relationship between the gyrification index of the right supramarginal gyrus (SupraMG) and WAIS-III Digit Symbol test scores was observed in older adult participants (r=0.375; P<0.001; 95% CI for r values 0.203–0.522).

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**Conclusions:** The results suggest that, compared with males, females have more extensive differences in cortical morphology. The gyrification index of the right SupraMG can be used as an imaging marker of sexual cognitive differences between males and females in older adults. This study helps to further understand sex differences in the aging of the brain and cognition.

**Keywords:** Aging; cortical morphology; sex difference; processing speed; working memory; structural magnetic resonance imaging (sMRI)

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## Introduction

Human brain structures are not static across the lifespan but exhibit morphology changes with age, which are possibly linked to neurodevelopment or neurodegeneration (1,2). These changes impact cognitive performance. Cortical gray matter (GM) structure significantly reduces with age at multiple locations, including the frontal and temporal lobes, insular areas, and cerebellum (3-8). Age effects on the brain structures related to cognitive function may be important for understanding the role of aging in mild cognitive impairment (MCI) and Alzheimer disease (AD) (9-13). For instance, the decrease in episodic memory is related to volume alterations of the entorhinal cortex in healthy older adults (14). Executive function deficits in healthy aging are associated with greater atrophy of the prefrontal regions (15). Additionally, several studies have documented anatomical differences in the brain across the sexes. Epidemiological studies have shown that females have a higher risk of developing AD, but the reasons why are unclear (16). In particular, there is some evidence for the cerebral cortex imaging markers of sex differences in the aging process. A study of the thinning of the cerebral cortex during aging found that global thickness thinning was apparent by middle age (1). Males and females showed a similar degree of global thinning and did not differ in mean thickness in the younger or older groups (1). Another study showed that males and females have different age trajectories regarding changes in brain structures; males over 45 years old showed an earlier acceleration of change in global and lobar volumes compared with females (16). In addition, age-related subcortical volume reductions are more rapid among males. For example, in one study, compared with females at approximately 70 years old, males showed a steeper reduction in thalamic volume (after 25 years of age) and a faster hippocampus atrophy speed (17). Two studies have shown that males have larger brains than do females (18,19). In contrast, other studies have observed greater cortical thickness in females than in males (20,21). One study also observed a significantly greater global cortical thickness in healthy young females than in males (22). However, the influence of sex on brain aging and cognitive changes remains unclear, especially in the transition from middle age to older adulthood. Therefore, systematic research of the sex differences in brain structure and cognition among middle-aged and older adults groups could deepen our understanding of the healthy aging of the brain structure and provide a clearer understanding of the possible neuroanatomical differences between sexes.

However, to date, previous studies have mainly used the voxel-based morphometry (VBM) method to analyze structural brain differences in aging and sex (5,7,23,24). This method is not particularly suited for considering intersubject macro-anatomical modifiability in gyral and sulcal folding patterns and the specific brain tissue property behind the differences in GM density (25). Surface-based morphometry (SBM) offers more information for brain structural analysis. The SBM approach provides measurements of several GM properties, including cortical thickness, gyrification index, and surface complexity, that potentially play different roles in brain function (26,27). Cortical thickness is estimated as the distance between the gray–white boundary and the outer cortical surface (28). The gyrification index is a metric that quantifies the amount of cortex buried within the sulcal folds compared to the amount of cortex on the outer cortex (29). Surface complexity is represented by the fractal dimension, which may be seen as an estimation of gyrification, through a combination of sulcal depth, the frequency of cortical folding, and the convolution of gyral shape (30). These measures have been successfully used to study aging

 

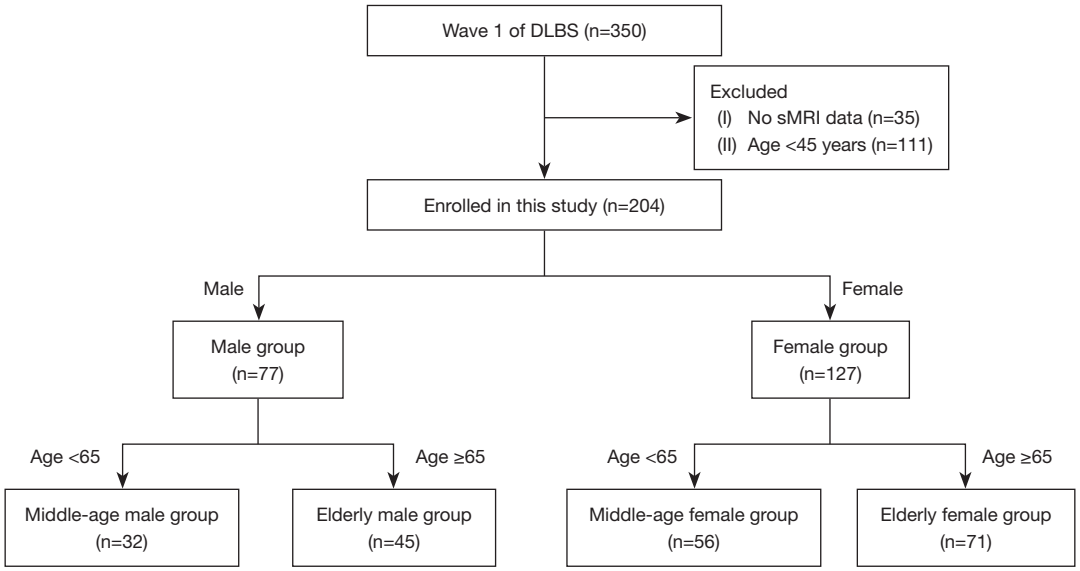


**Figure 1** Participant selection flowchart. DLBS, Dallas Lifespan Brain Study; sMRI, structural magnetic resonance imaging.

(1,31,32), AD (33,34), sex differences, and cognitive functioning (35). The advantage of SBM over the VBM method is that SBM is theoretically quantitative because it measures and compares absolute distances and shapes rather than magnetic resonance imaging (MRI) intensities (2).

We used the SBM technique to conduct a cross-sectional study that evaluated sex and age differences and age and sex interactions and their relationships with cortical morphology differences (cortical thickness, gyrification index, and surface complexity) in middle-aged and older adult participants. In addition, we further investigated the correlation between cortical morphology differences and processing speed and working memory to explore the possible influence of cortical morphology changes on cognitive function. We present the following article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-22-583/rc).

## Methods

### *Participants*

Participants were selected from wave 1 of the Dallas Lifespan Brain Study (DLBS). As an initiative of the Center for Vital Longevity, School of Behavioral and Brain Sciences at the University of Texas in Dallas, the DLBS is a major effort designed to understand the antecedents of preservation and decline of cognitive function at different stages of the adult lifespan. Wave 1 of the DLBS data collection was completed from 2008 to 2014. The data are available on the International Neuroimaging Data-sharing Initiative, including apolipoprotein E gene information, cognitive tests, structural MRI, and positron emission tomography (PET) data (from https://fcon_1000.projects.nitrc.org/indi/retro/dlbs.html). The participants comprised 315 healthy adults (198 females; 117 males) aged 20–89 years. The Mini-Mental State Examination (MMSE) served as a general cognitive function test. All participants had an MMSE score greater than or equal to 26 and 12 or more years of education. All were native English speakers and right-handed. Participants were excluded if screening showed that they had experienced neurologic or psychiatric disorders, loss of consciousness for more than 10 min, drug or alcohol abuse, major heart surgery, or chemotherapy within 5 years of DLBS. Finally, 204 participants aged 45 years and older (127 females; 77 males) were included in the current study. Analyses were stratified by 2 age groups: 45–64 years (middle-aged adults) and 65 years or older (older adults) (36). The participants were classified into four groups: middle-aged males (n=32), middle-aged females (n=56), older adult males (n=45), and older adult females (n=71; *Figure 1*). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The basic information of these participants is shown in *Table 1*.

 

**Table 1** Sample characteristics

| Characteristics | Middle-aged males | Middle-aged females | Older adult males | Older adult females | F value | P value |
|---|---|---|---|---|---|---|
| Age (years)[#] | 54.00±5.85 | 55.38±5.50 | 75.90±7.27 | 76.56±6.78 | 185.594[&] | <0.001*** |
| Number of participants | 32 | 56 | 45 | 71 | n.d. | n.d. |
| Education (years)[#] | 16.66±2.38 | 16.76±1.99 | 17.07±2.35 | 16.09±2.59 | 1.752[&] | 0.158 |
| Race | | | | | | |
| White/Caucasian | 25 | 52 | 44 | 68 | – | – |
| Black/African American | 2 | 2 | – | 1 | – | – |
| American Indian/Alaskan Native | 1 | – | – | 2 | – | – |
| Multiracial | 3 | 1 | – | – | – | – |
| Other | 1 | 1 | 1 | – | – | – |
| MMSE scores[#] | 28.55±1.17 | 28.38±1.16 | 28.00±1.25 | 27.31±1.13 | 9.968[&] | <0.001*** |
| DC[#] | 67.68±10.80 | 64.41±11.90 | 55.79±11.96 | 51.27±10.21 | 22.42[&] | <0.001*** |
| DS[#] | 59.55±9.00 | 58.22±11.19 | 47.50±10.83 | 41.27±10.19 | 33.56[&] | <0.001*** |
| LNS[#] | 12.41±3.35 | 11.77±3.09 | 9.49±2.13 | 9.59±2.56 | 13.46[&] | <0.001*** |
| CANTAB-SWM[#] | 23.66±18.27 | 30.89±16.28 | 40.56±22.72 | 46.49±19.38 | 13.28[&] | <0.001*** |

[#], data are presented as mean ± standard deviation; [&], one-way ANOVA (analysis of variance); ***, P<0.001. n.d., not done; MMSE, mini-mental state examination; DC, digit comparison; DS, Wechsler Adult Intelligence Scale-III digit symbol; LNS, Wechsler Adult Intelligence Scale-III Letter-Number Sequencing; CANTAB-SWM, Cambridge Neuropsychological Test Automated Battery Spatial Working Memory.

### *Neuropsychological examination for cognitive function*

All participants in the present study were evaluated with a battery of neuropsychological tests. These tests were used to assess 2 cognitive domains: the speed of processing and working memory. The Digit Comparison (DC) (37) Task and Wechsler Adult Intelligence Scale third edition (WAIS-III) Digit Symbol (DS) (38) were used to evaluate the speed of processing. Working memory function was assessed using the WAIS-III Letter-Number Sequencing (LNS) (38) and Cambridge Neuropsychological Test Automated Battery (CANTAB) Spatial Working Memory (SWM) tests (39). Details on the cognitive function tests are available online (https://sites.utdallas.edu/dlbs/data-collection).

### *Structural MRI data acquisition*

All structural MRI data images were collected using the DLBS with a Philips Achieva 3.0 T MR scanner with an 8-channel head coil. High-resolution T1-weighted, sagittal 3D magnetization-prepared rapid gradient-echo (MP-RAGE) sequences were acquired and covered the entire brain. The parameters used were as follows: 160 sagittal slices, repetition time (TR) =8.1 ms, echo time (TE) =3.7 ms, slice thickness =1 mm, flip angle =12°, field of view (FOV) =204×256 $mm^2$, and acquisition matrix =256×256.

### *Imaging processing*

We used the CAT12 toolbox (revision 1830, http://dbm.neuro.uni-jena.de/cat/) for SPM12 (revision 7771; http://www.fil.ion.ucl.ac.uk/spm/software/spm12/) for segmentation of all 3D-T1 images. The CAT12 toolbox runs within SPM12; that is, SPM12 must be installed and added to the Matlab search path before the CAT12 toolbox can be installed. Structural MRI processing in CAT12 can be separated into two main processes: voxel-based processing and surface-based processing. Voxel-based processing comprises skull-stripping of the brain, spatial adaptive nonlocal means denoising filter, bias correction,

 

**Table 2** The pairwise comparisons of sample characteristics between the four groups

| Characteristics | G1 *vs.* G2 | G1 *vs.* G3 | G1 *vs.* G4 | G2 *vs.* G3 | G2 *vs.* G4 | G3 *vs.* G4 |
|---|---|---|---|---|---|---|
| Age (years) | 1.000 | <0.001*** | <0.001*** | <0.001*** | <0.001*** | 1.000 |
| Education (years) | 1.000 | 1.000 | 1.000 | 1.000 | 0.707 | 0.192 |
| MMSE scores | 1.000 | 0.059 | <0.001*** | 0.842 | 0.001** | 0.016* |
| DC | 1.000 | <0.001*** | <0.001*** | 0.002** | <0.001*** | 0.219 |
| DS | 1.000 | <0.001*** | <0.001*** | <0.001*** | <0.001*** | 0.011* |
| LNS | 1.000 | <0.001*** | <0.001*** | <0.001*** | <0.001*** | 1.000 |
| CANTAB-SWM | 0.546 | 0.001** | <0.001*** | 0.077 | <0.001*** | 0.640 |

The expressed data are P values of the pairwise comparisons between groups under Bonferroni correction. *, P<0.05; **, P<0.01; ***, P<0.001. G1, middle-aged male group; G2, middle-aged female group; G3, older adult male group; G4, older adult female group. MMSE, mini-mental state examination; DC, digit comparison; DS, Wechsler Adult Intelligence Scale-III Digit Symbol; LNS, Wechsler Adult Intelligence Scale-III Letter-Number Sequencing; CANTAB-SWM, Cambridge Neuropsychological Test Automated Battery Spatial Working Memory.

and affine registration. The images were then segmented into GM, white matter (WM), and cerebrospinal fluid (CSF), and the tissue segments were spatially normalized to Montreal Neurological Institute (MNI) standard space using diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL) (40). In the surface-based processing, the cortical thickness estimation and reconstruction of the central surface were conducted using a projection-based thickness method (28). Subsequently, surface reconstruction, topological correction, and surface refinement were performed, which resulted in the central surface mesh (41). The individual central surfaces were spatially registered to the FsAverage template in FreeSurfer (Laboratory for Computational Neuroimaging at the Athinoula A. Martinos Center for Biomedical Imaging), and then the local thickness values were transferred onto the same template. Cortical thickness measurements were obtained by reconstructing representations of the GM/WM boundary. The gyrification index was defined as the ratio between the inner surface size to the outer surface size of a convex hull (29,30). Following this, the cortical thickness, fractal dimension, and gyrification index of each participant in the standard space were obtained. Finally, cortical thickness maps were smoothed with a 15 mm full width at half maximum of the Gaussian smoothing kernel, and fractal dimension and gyrification index maps were smoothed at 20 mm (Figure S1). All structural images were visually inspected after the automated analyses to assess appropriate segmentation and labeling by a single user, and all data passed this quality control.

### *Statistical analysis*

In this cross-sectional study, the middle-aged and older adult participants were divided into four groups: middle-aged males, middle-aged females, older adult males, and older adult females. Age, education years, MMSE, DC, DS, LNS, and CANTAB-SWM scores are presented as mean ± standard deviation for each group. Differences in age, education years, and cognitive tests score were evaluated using the 1-way analysis of variance (ANOVA) test (*Table 1*). For indices with significant differences across the four groups, we examined the post hoc differences. Pairwise comparisons across all participants for age, education years, and cognitive tests were evaluated using Bonferroni correction (P<0.05) for multiple comparisons (*Table 2*). Comparisons of cortical morphology differences were calculated by 2-way ANOVA as implemented in CAT12 using education years as a covariate (42). The dependent variables in this study were the cortical thickness, fractal dimension, and gyrification index. The independent variables in this study were the (I) 2 levels of sex, males and females, and (II) the 2 levels of age, middle-aged and older adults. Subsequently, we analyzed the main age effect and the main sex effect separately. Finally, we calculated cortical morphology differences between the middle-aged and older adult groups based on the main effect of age, and the differences between the males and females based on the main effect of sex. All obtained clusters of each comparison were corrected post hoc by an extent threshold of 100 contiguous vertices and reported after family-wise error (FWE) correction on a cluster level of a 5% alpha error.

 

Spearman correlation coefficient was used to investigate the association between cortical morphology differences and cognitive test scores. The correlation tests were considered significant at a threshold of P<0.05 with the false discovery rate (FDR) correction. Statistical analysis was performed with SPSS version 25.0 (IBM Corporation, Armonk, NY, USA).

## Results

### *Demographic and cognitive function*

The demographic and cognitive test scores of participants for each group are presented in *Table 1*, and the pairwise comparisons of demographic and cognitive test scores between the four groups are listed in *Table 2*. The four groups of individuals did not differ with respect to years of education (F=1.752; P=0.158); However, they did differ in average scores of MMSE (F=9.968; P<0.001), DC (F=22.42; P<0.001), DS (F=33.56; P<0.001), LNS (F=13.46; P<0.001), and CANTAB-SWM (F=13.28; P<0.001). Compared to older adult participants, the middle-aged group showed higher scores on MMSE, DC, DS, and LNS, and lower scores on CANTAB-SWM. There were no significant differences in any of the cognitive tests between the two middle-aged groups, whereas MMSE (P=0.016) and DS (P=0.011) scores were significantly different between the two groups of older adults. These scores were higher in the older adult male group than in the older adult female group.

### *Brain structure*

There was no significant interaction effect in cortical thickness, fractal dimension, or gyrification index. However, we observed a significant main age effect in cortical thickness, fractal dimension, and gyrification index, as well as main sex effect in fractal dimension and gyrification index.

#### Cortical thickness

A significant main effect of age on cortical thickness was observed (*Figure 2* and Table S1). The post hoc results showed a significantly thinner cortical thickness in the older adult male group, mainly including the bilateral superior frontal gyrus (SFG), superior temporal gyrus (STG), rostral middle frontal gyrus (rMFG), transverse temporal gyrus (TTG), postcentral gyrus (PostCG), lingual gyrus (LG), the left precentral gyrus (PreCG), and precuneus (PreCUN), compared with that of the middle-aged male group. As further illustrated in *Figure 2* (second and third columns) and *Table 3*, compared with the male group, females showed significant differences in cortical thickness related to aging in almost the whole brain, with more pronounced aging effects on cortical thickness in the female group than in the male group.

#### Fractal dimension

The fractal dimension in the middle-aged female group was significantly higher than that of the older adult female group bilaterally in the insula (INS), in the lateral orbitofrontal gyrus (LFGor), and inferior temporal gyrus (ITG) in the right hemisphere. The middle-aged males had significantly higher surface complexity in the left STG compared to the older adult males. In addition, we detected significant sex differences between the middle-aged female and middle-aged male groups for the fractal dimension in the fusiform gyrus (FG) and LG in the right hemisphere. These regions are highlighted in *Figure 3*, *Table 4*, and Table S2 and Table S3.

#### Gyrification index

Compared with the older adult male group, the middle-aged male group had a higher gyrification index in the bilateral INS and pars opercularis (pOPER) and the right PreCG. There were also significant differences between the 2 female groups for the gyrification index in both hemispheres. The gyrification index was higher for the bilateral STG, INS, supramarginal gyrus (SupraMG), TTG, pars triangularis (pTRI), pOPER, and right PreCG and lower for the left isthmus cingulate (IC) in the middle-aged female group. Furthermore, significant sex differences between the older adult male and older adult female groups were also detected. The gyrification index was higher for the bilateral caudal middle frontal gyrus (cMFG), rMFG, SFG, and right lateral occipital gyrus (LOG) and lower for the right SupraMG in the older adult female group. These regions are highlighted in *Figure 4*, *Table 5*, and Table S4 and Table S5.

### *Correlation results*

The relationship between cortical morphology and cognitive ability is shown in *Figure 5*. During the aging process, females showed more significant positive correlations between the cortical thickness of the right SFG and LNS test scores (females: r=0.394; P<0.001; 95% CI for r values 0.216–0.577; *Figure 5A*) than did males (males: r=0.344;

 

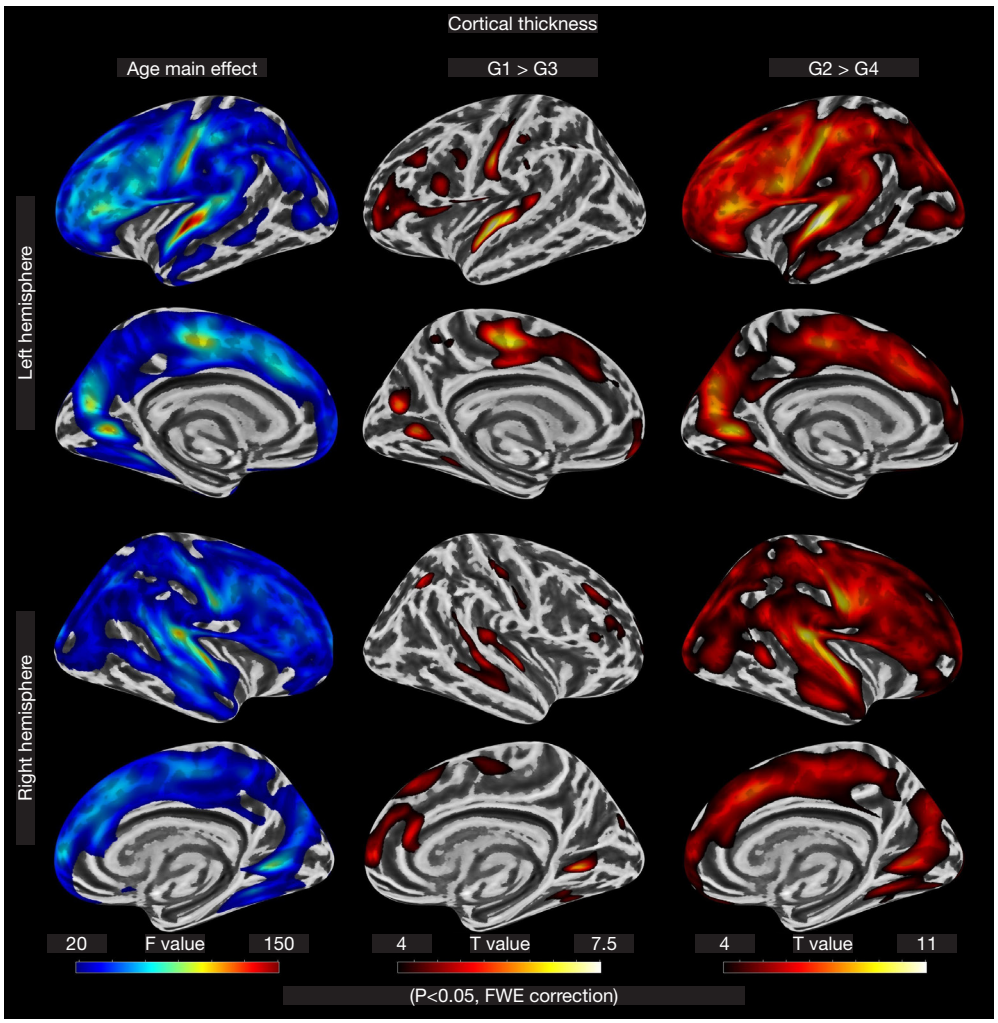


**Figure 2** Age and sex differences in cortical thickness changes. G1, middle-aged male group; G2, middle-aged female group; G3, older adult male group; G4, older adult female group; FWE, family-wise error.

P<0.001; 95% CI for r values 0.197–0.491; *Figure 5B*). In addition, a significant relationship between the gyrification index of the right SupraMG and DS test scores was observed in the older adult groups (r=0.375; P<0.001; 95% CI for r values 0.203–0.522; *Figure 5C*). However, there was no significant correlation found between fractal dimension and cognitive function in this study.

## Discussion

Based on the DLBS cohort, this study explored the differences in cortical morphology of middle-aged and older adults and evaluated the relationship between the cortical thickness, gyrification index, fractal dimension, cognitive abilities during the aging process and sex differences. The study made three main findings. First, cortical morphology and cognitive abilities show significant age associations, and general cognitive function, speed of processing, and working memory were significantly decreased in older adults compared with middle-aged adults. The cortical morphology of SFG, MFG, PCC, INS, PreCUN, TTG, STG, PreCG, and PostCG changed significantly with aging. Furthermore, there were significant positive correlations between the cortical thickness of the right SFG and LNS test scores. Second, there were significant differences in fractal dimension and gyrification index between sexes but no significant differences in cortical thickness. Sex differences in the fractal dimension were

 

**Table 3** The pairwise comparisons of cortical thickness between the four groups

| Comparison between two groups | Hemisphere | Overlap of atlas region | Cluster size (vertices) | Peak MNI coordinate | | | t value | P value (FWE) |
|---|---|---|---|---|---|---|---|---|
| | | | | x | y | z | | |
| G1 > G3 | Left | 57% SFG; 27% ParaCG; 16% PCC | 5,455 | –10 | –18 | 46 | 6.5 | <0.001*** |
| | | 71% STG; 23% TTG; 6% INS | 3,345 | –46 | –19 | –3 | 7.1 | <0.001*** |
| | | 59% rMFG; 27% pTRI; 13% pOPER; 1% pORB | 3,291 | –36 | 52 | 14 | 5.1 | 0.001** |
| | | 83% PostCG; 17% PreCG | 1,896 | –50 | –12 | 28 | 6.2 | <0.001*** |
| | | 35% MFGor; 27% SFG; 25% Fpole; 10% rMFG; 3% LFGor | 895 | –5 | –57 | –12 | 5.0 | 0.002** |
| | | 82% LG; 18% PeriCAL | 819 | –18 | –68 | 2 | 5.9 | 0.002** |
| | | 64% CUN; 24% PreCUN; 12% PeriCAL | 783 | –11 | –67 | 14 | 5.8 | 0.003** |
| | | 94% pOPER; 3% cMFG; 3% rMFG | 712 | –42 | 13 | 25 | 5.0 | 0.004** |
| | | 87% rMFG; 13% cMFG | 637 | –42 | 28 | 35 | 4.9 | 0.008** |
| | | 49% PreCG; 33% pOPER; 18% PostCG | 521 | –44 | –6 | 12 | 4.7 | 0.010* |
| | | 71% PreCG; 29% cMFG | 428 | –46 | 0 | 31 | 4.8 | 0.039* |
| | | 100% PostCG | 317 | –47 | –27 | 42 | 4.8 | 0.004** |
| | | 57% LG; 34% FG; 9% ParaHIPP | 238 | –33 | –45 | –8 | 4.8 | 0.005** |
| | | 100% PreCUN | 151 | –6 | –55 | 51 | 4.4 | 0.020* |
| | | 100% SupraMG | 107 | –62 | –29 | 31 | 4.4 | 0.024* |
| | Right | 68% SFG; 12% CAR; 11% rMFG; 9% RAC | 2,927 | 9 | 52 | 7 | 5.4 | <0.001*** |
| | | 40% STG; 31% MTG; 23% bSTS; 6% SupraMG | 2,449 | 51 | –30 | 0 | 5.3 | 0.001** |
| | | 50% STG; 31% TTG; 15% SupraMG; 4% INS | 1,996 | 44 | –21 | –2 | 5.6 | <0.001*** |
| | | 100% SFG | 1,337 | 6 | 29 | 49 | 5.1 | 0.001** |
| | | 84% LG; 16% PeriCAL | 804 | 19 | –60 | 2 | 6.1 | <0.001*** |
| | | 94% IPG; 6% SPG | 794 | 35 | –62 | 46 | 5.3 | 0.001** |
| | | 91% rMFG; 9% cMFG | 749 | 35 | 30 | 40 | 5.0 | 0.002** |
| | | 100% rMFG | 745 | 43 | 39 | 23 | 4.7 | 0.007** |
| | | 97% PostCG; 3% PreCG | 736 | 41 | –18 | 47 | 4.8 | 0.004** |
| | | 60% ParaCG; 40% SFG | 638 | 6 | –7 | 57 | 4.6 | 0.008** |
| | | 88% FG; 11% LG; 1% ParaHIPP | 576 | 33 | –51 | –7 | 4.7 | 0.006** |
| | | 94% PostCG; 6% PreCG | 315 | 52 | –10 | 25 | 4.5 | 0.013* |
| | | 86% CUN; 14% SPG | 189 | 4 | –81 | 32 | 4.4 | 0.020* |
| | | 80% pTRI; 20% rMFG | 186 | 47 | 31 | 12 | 4.6 | 0.010* |

**Table 3** *(continued)*

**Table 3** *(continued)*

| Comparison between two groups | Hemisphere | Overlap of atlas region | Cluster size (vertices) | Peak MNI coordinate | | | t value | P value (FWE) |
|---|---|---|---|---|---|---|---|---|
| | | | | x | y | z | | |
| G2 > G4 | Left | 16% SFG; 8% PreCG; 8% SPG; 8% PostCG; 8% SupraMG; 7% rMFG; 6% STG; 6% IPG; 5% PreCUN; 4% cMFG; 3% LOG; 3% pOPER; 3% LG; 2% LFGor; 2% pTRI; 2% ParaCG; 2% PCC; 2% INS; 1% PeriCAL; 1% FG; 1% MTG; 1% CUN; 1% TTG | 98,332 | –46 | –18 | 1 | 10.8 | <0.001*** |
| | | 87% MTG; 13% bSTS | 915 | –64 | –44 | –6 | 5.5 | <0.001*** |
| | Right | 17% SFG; 9% PreCG; 8% SPG; 8% IPG; 8% PostCG; 8% rMFG; 7% SupraMG; 6% STG; 4% LOG; 4% cMFG; 3% MTG; 3% PreCUN; 3% ParaCG; 2% pOPER; 2% LG; 2% pTRI; 2% LFGor; 1% PCC; 1% PeriCAL; 1% INS; 1% CUN | 97,215 | 42 | –34 | 13 | 9.9 | <0.001*** |

*, P<0.05; **, P<0.01; ***, P<0.001. G1, middle-aged male group; G2, middle-aged female group; G3, older adult male group; G4, older adult female group. SFG, superior frontal gyrus; ParaCG, paracentral gyrus; PCC, posterior cingulate; STG, superior temporal gyrus; TTG, transverse temporal gyrus; INS, insula; rMFG, rostral middle frontal gyrus; pTRI, pars triangularis; pOPER, pars opercularis; pORB, pars orbitalis; PostCG, postcentral gyrus; PreCG, precentral gyrus; MFGor, rostral middle frontal gyrus; Fpole, frontal pole; rMFG, rostral middle frontal gyrus; LFGor, lateral orbitofrontal gyrus; LG, lingual gyrus; PeriCAL, pericalcarine cortex; cMFG, caudal middle frontal gyrus; FG, fusiform gyrus; ParaHIPP; parahippocampal gyrus; SupraMG, supramarginal gyrus; IPG, inferior parietal gyrus; RAC, rostral anterior cingulate; CAR, caudal anterior cingulate; MTG, middle temporal gyrus; bSTS, banks of the superior temporal sulcus; SPG, superior parietal gyrus; LOG, lateral occipital gyrus; CUN, cuneus; PreCUN, precuneus; MNI, Montreal Neurological Institute; FWE, family-wise error.

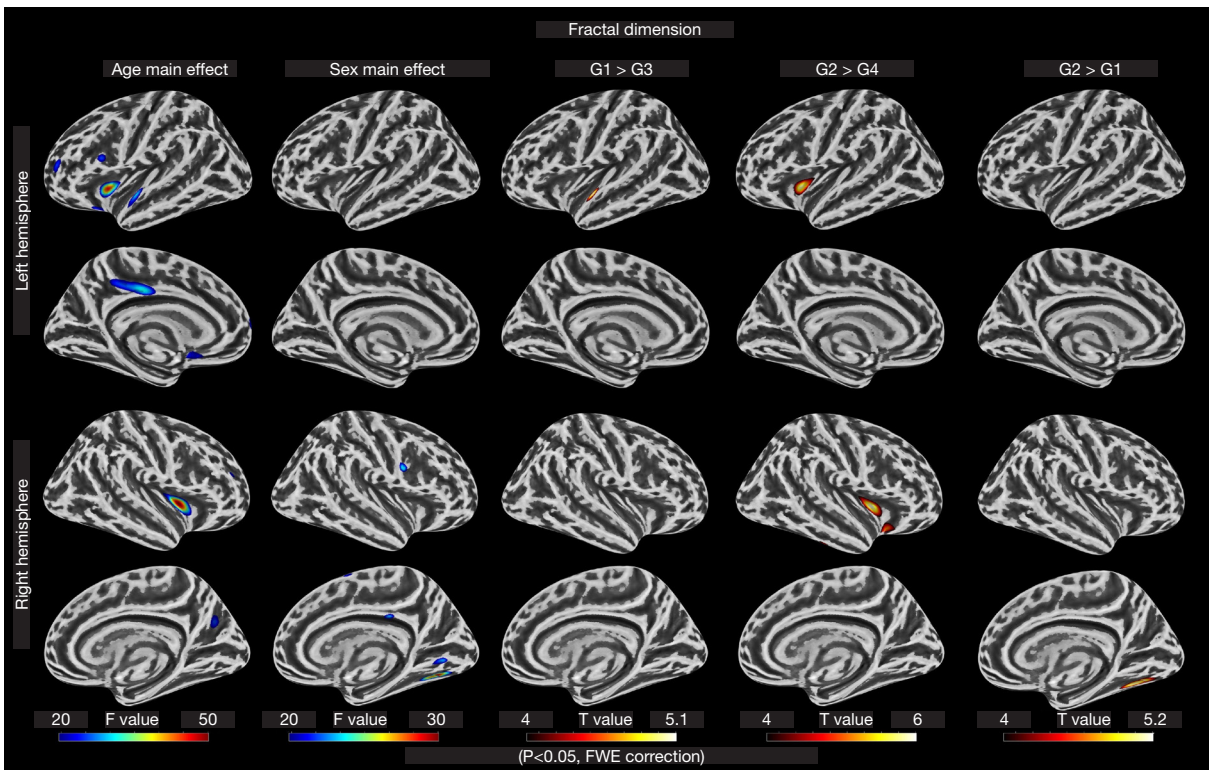


**Figure 3** Age and sex differences in fractal dimension changes. G1, middle-aged male group; G2, middle-aged female group; G3, older adult male group; G4, older adult female group; FWE, family-wise error.

 

**Table 4** The pairwise comparisons of the fractal dimension between the four groups

| Comparison between two groups | Hemisphere | Overlap of atlas region | Cluster size (vertices) | Peak MNI coordinate | | | t value | P value (FWE) |
|---|---|---|---|---|---|---|---|---|
| | | | | x | y | z | | |
| G1 > G3 | Left | 99% STG; 1% TTG | 270 | –51 | –6 | –3 | 5.1 | 0.002** |
| G2 > G4 | Left | 100% INS | 528 | –35 | 7 | 3 | 5.9 | <0.001*** |
| | Right | 100% INS | 645 | 36 | 4 | 6 | 6.0 | <0.001*** |
| | | 62% INS; 38% LFGor | 433 | 31 | 17 | –11 | 5.3 | 0.001** |
| | | 100% ITG | 112 | 50 | –29 | –27 | 4.6 | 0.011* |
| G2 > G1 | Right | 80% FG; 20% LG | 571 | 28 | –68 | –6 | 5.2 | 0.001** |

*, P<0.05; **, P<0.01; ***, P<0.001. G1, middle-aged male group; G2, middle-aged female group; G3, older adult male group; G4, older adult female group. STG, superior temporal gyrus; TTG, transverse temporal gyrus; INS, insula; LFGor, lateral orbitofrontal gyrus; ITG, inferior temporal gyrus; FG, fusiform gyrus; LG, lingual gyrus; MNI, Montreal Neurological Institute; FWE, family-wise error.

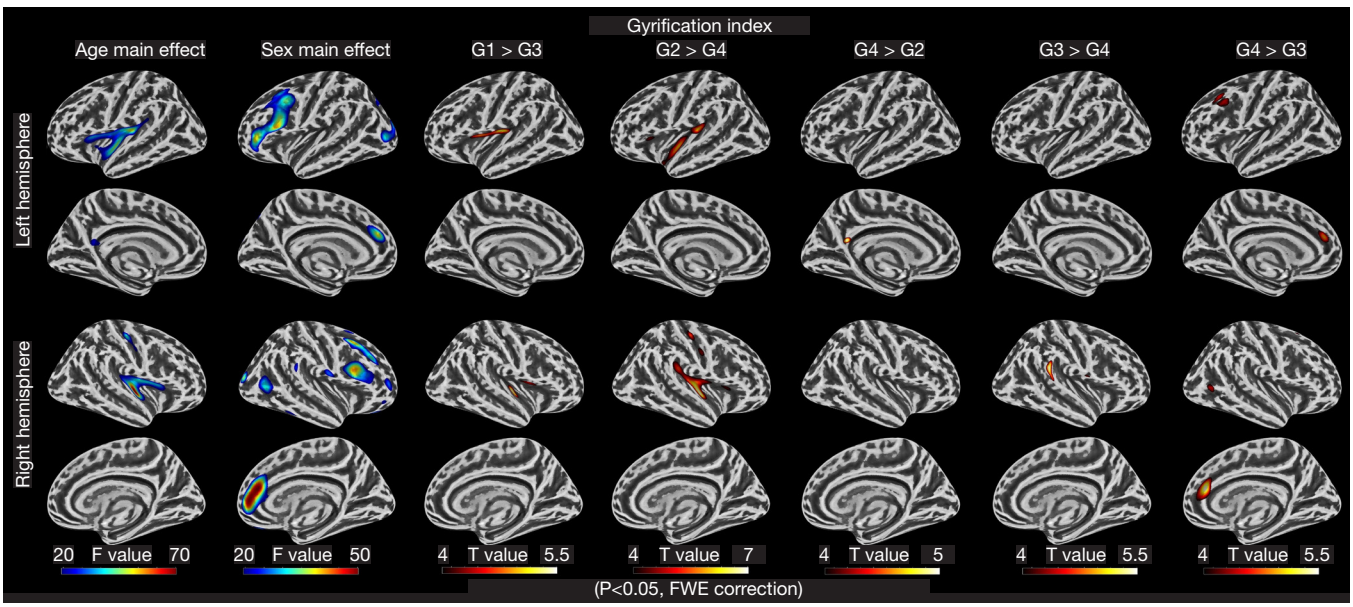


**Figure 4** Age and sex differences in gyrification index changes. G1, middle-aged male group; G2, middle-aged female group; G3, older adult male group; G4, older adult female group; FWE, family-wise error.

found in the middle-aged group, and gyrification index differences were found in the older group. Notably, a significant relationship between the gyrification index of the right SupraMG and DS scores was observed in the older groups. Third, results relating to cortical thickness, fractal dimension, or gyrification index showed that cortical differences in females were more affected by aging than were those in males.

### *Differences in cognitive function*

The present study explored the differences in cognitive function in middle-aged and older adult participants from two aspects: speed of processing and working memory. Processing speed and working memory are mechanisms that play important explanatory roles in the age-related decline of cognitive abilities (43). The processing-speed

**Table 5** The pairwise comparisons of the gyrification index between the four groups

| Comparison between two groups | Hemisphere | Overlap of atlas region | Cluster size (vertices) | Peak MNI coordinate | | | t value | P value (FWE) |
|---|---|---|---|---|---|---|---|---|
| | | | | x | y | z | | |
| G1 > G3 | Left | 86% INS; 10% pOPER; 4% TTG | 1,286 | –35 | –19 | 19 | 5.0 | 0.002** |
| | Right | 51% STG; 48% INS; 1% TTG | 444 | 40 | –23 | –1 | 5.2 | 0.001** |
| | | 54% PreCG; 28% pOPER; 15% INS; 3% PostCG | 268 | 37 | 5 | 13 | 4.5 | 0.015* |
| G2 > G4 | Left | 56% STG; 44% INS | 1,414 | –41 | –19 | –8 | 5.9 | <0.001*** |
| | | 28% INS; 27% SupraMG; 23% TTG; 22% STG | 1,066 | –35 | –33 | 15 | 5.9 | <0.001*** |
| | | 60% pTRI; 40% pOPER | 167 | –33 | 23 | 10 | 4.7 | 0.010* |
| | Right | 40% INS; 35% SupraMG; 13% STG; 11% TTG | 3,723 | 43 | –22 | –2 | 6.7 | <0.001*** |
| | | 100% PreCG | 445 | 35 | –22 | 47 | 5.4 | <0.001*** |
| | | 96% PreCG; 4% PostCG | 271 | 43 | –10 | 31 | 4.8 | 0.006** |
| | | 52% pOPER; 33% INS; 15% pTRI | 144 | 33 | 19 | 11 | 4.6 | 0.015* |
| G4 > G2 | Left | 98% IC; 2% PreCUN | 152 | –4 | –50 | 18 | 4.7 | 0.013* |
| G3 > G4 | Right | 71% SupraMG; 21% STG; 8% bSTS | 643 | 63 | –41 | 21 | 5.0 | 0.002** |
| G4 > G3 | Left | 96% cMFG; 4% rMFG | 397 | –44 | 19 | 38 | 4.5 | 0.017* |
| | | 91% cMFG; 9% rMFG | 376 | –33 | 22 | 48 | 4.6 | 0.013* |
| | | 100% SFG | 231 | –12 | 39 | 20 | 4.9 | 0.004** |
| | Right | 51% SFG; 34% rMFG; 15% cMFG | 770 | 12 | 36 | 17 | 5.3 | 0.001** |
| | | 44% IPG; 43% LOG; 13% MTG | 181 | 44 | –64 | 5 | 4.6 | 0.013* |

*, P<0.05; **, P<0.01; ***, P<0.001. G1, middle-aged male group; G2, middle-aged female group; G3, older adult male group; G4, older adult female group. INS, insula; pOPER, pars opercularis; TTG, transverse temporal gyrus; STG, superior temporal gyrus; PreCG, precentral gyrus; PostCG, postcentral gyrus; SupraMG, supramarginal gyrus; pTRI, pars triangularis; IC, isthmus cingulate; PreCUN, precuneus; bSTS, banks of the superior temporal sulcus; cMFG, caudal middle frontal gyrus; rMFG, rostral middle frontal gyrus; SFG, superior frontal gyrus; IPG, inferior parietal gyrus; LOG, lateral occipital gyrus; MTG, middle temporal gyrus; MNI, Montreal Neurological Institute; FWE, family-wise error.

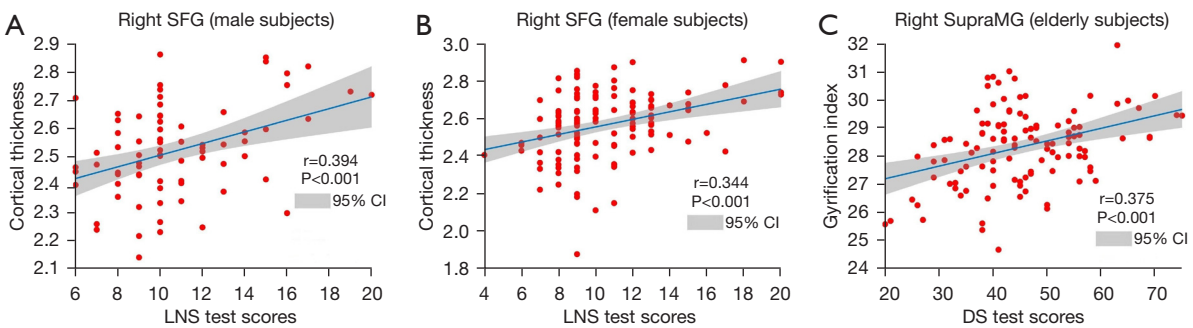


**Figure 5** Relationships between the measures of cortical morphology and cognitive function. (A) Cortical thickness of the right SFG was significantly associated with the WAIS-III LNS test scores in males. (B) Cortical thickness of the right SFG was significantly associated with LNS test scores in females. (C) The gyrification index of the right SupraMG was significantly associated with WAIS-III DS test scores in older adult participants. SFG, superior frontal gyrus; WAIS, Wechsler Adult Intelligence Scale; LNS, Letter-Number Sequencing; SupraMG, supramarginal gyrus; DS, Digit Symbol. Units: Cortical thickness (mm); gyrification index (dimensionless).

theory indicates that a major factor contributing to age-related differences in memory and other aspects of cognitive functioning is a reduction with increased age in the speed with which many cognitive operations can be executed (44). Processing speed performance, especially inspection time, might be useful as a biological marker of cognitive aging (43). In the present study, DC and DS tests were used to evaluate the processing speed of middle-aged and older adult participants. Consistent with previous studies, we found that processing speed declined on average as people grew older (P<0.001) (45-48). Both verbal working memory (LNS test) and spatial working memory (CANTAB-SWM test) showed significant differences between the middle-aged group and the older adult group (P<0.001). Furthermore, we found that a thinner right SFG was related to worse working memory in aging. Older adults show working memory deficiencies and slowing due to the selection of irrelevant information into the contents of working memory, along with inefficient deletion of working memory contents that are no longer relevant to task performance (49). According to previous studies, females in their 60s show a significantly faster age-related decline and greater deterioration of cognition than do men (50,51). Our results also indicated the same trend, especially in processing speed. We found significant sex differences in the DS test in the older adult group (older adult males: 47.50±10.83; older adult females: 41.27±10.19; P=0.011). In contrast, there was no significant difference in working memory between different sexes during aging. Studies on sex differences in working memory in middle-aged and older adults people often report conflicting results. Some studies have found that males have advantages in verbal and visuospatial working memory (52,53). In contrast, other studies have reported that females have advantages in these aspects or that there are no sex differences in verbal working memory and visuospatial working memory (54,55). These inconsistent findings might be due to methodological differences, such as in sample size, age groups, and working memory tasks. Overall, in this study, the cognitive level of females was slightly lower than that of males. However, age was found to be a more important factor than sex in the cognitive changes of middle-aged and older adult participants.

### *Differences in cortical morphology and their relationship with cognition*

We here report on the age and sex differences in cortical thickness, fractal dimension, and gyrification index. We found no significant age-sex interaction effect for these morphological differences. However, we observed that these parameters changed significantly with age. Numerous studies have identified widespread age-related reductions in cortical thickness. Madan (56) found that age-related differences in brain structure are systematic enough to enable reliable age prediction based on metrics of cortical morphology. The strongest consistent effects of age are reported for the prefrontal, temporal, and parietal regions (57-61). Consistent with these studies, we found that the cortical thickness of older adult participants decreased significantly in the whole brain, excluding the occipital lobe and mainly including the SFG, rMFG, STG, middle temporal gyru (MTG), superior parietal gyrus (SPG), inferior parietal gyrus (IPG), and LG. Furthermore, significant age differences were found in the cortical thickness of PreCG, PostCG, and INS, which were considered insensitive to age in previous studies (58,60). In addition, the decrease in cortical thickness during the aging process was more prominent in females than in males. Of the studies that have examined the relationship between cortical thickness and cognition in cognitively healthy older adults, most have reported positive correlations between regional thickness and cognitive performance. For example, a study found that a thicker IFG and INS were related to better letter fluency while a greater thickness of other frontal regions and the IPG was positively correlated with category fluency (62). Westlye *et al.* (63) reported that anterior cingulate cortex and right IFG cortical thickness was correlated with the attention function. Sun *et al.* (64) reported that the thickness of the anterior temporal, rostral medial prefrontal, and anterior midcingulate cortex was correlated with memory performance. Similarly, we found a significant positive correlation between the thickness of the right SFG and verbal working memory in this study. Research has also linked working memory changes to age-related changes in the prefrontal cortex (PFC), a region important for working memory (65). The decline of working memory in the middle-aged and older adults is related to the thinning of SFG cortical thickness, which is consistent with the explanation of the hemispheric asymmetry reduction in older adults (HAROLD) model (66). Findings in support of the HAROLD model reveal that, during working memory tasks, young adults display left PFC activation during verbal working memory tasks, while older adults display bilateral activation of the PFC. Older adults compensate for age-related decline by recruiting additional neural networks to keep on the task; however,

 

with the gradual atrophy of the PFC in older adults, even if the bilateral PFC is activated, their working memory performance of still decreases significantly (66). However, no significant sex difference in cortical thickness was found in middle-aged or older adults.

Compared with widespread age-related reductions of cortical thickness, the differences in fractal dimension and gyrification index were regionally heterogeneous. The fractal dimension provides an important additional measure of brain structures that gives the means to consider differences in the shape of structures rather than the volume or thickness. Our findings differed from previous studies reporting that the GM fractal dimension is more sensitive to age-related differences (32,67). In this study, we only found that the fractal dimensions of the left STG in the male group and the bilateral INS and right ITG in the female group decreased significantly with age. An interesting finding of our study was that the fractal dimension of right FG and LG in middle-aged females was significantly higher than that in the male group, but this feature was not found in the older adult group. The lingual and fusiform gyri play important roles in visual processing. A previous study has shown that prosopagnosia is associated with damage to the fusiform and lingual gyri (68). Chao found that damage to the fusiform/lingual gyri correlates with a loss in color perception (69). This tentative finding of sex differences limited to the middle-aged group could suggest that the fractal dimension is influenced by sex hormones, as females are likely to undergo menopause during this period and thus experience an alteration in hormone levels. A recent study exploring the difference in spontaneous brain activity between premenopausal and perimenopausal females reported increased regional homogeneity value in the right LG in perimenopausal females compared with premenopausal females (70). Therefore, we speculate that the structural and functional differences of the right LG can be used as imaging markers of brain differences between middle-aged males and females. However, further research is needed to prove this speculation.

In the present study, gyrification index values changed during aging in the bilateral INS, TTG, and pOPER in both males and females. In addition, the gyrification index of the bilateral STG, pTRI, and SupraMG was only different between middle-aged and older adults females. These results suggest that the process of cortical aging is more complex in the female brain than it is in males. Compared with the differences in cortical thickness and fractal dimension, the gyrification index showed more sex differences but only in the older adult group. The gyrification index of the right SupraMG, STG, and bSTS was higher in older adult males than in the older adult female group In contrast, the gyrification index of the bilateral SFG, rMFG, and cMFG was higher in older females than in the the older adult male group. More importantly, a significant relationship between the gyrification index of the right SupraMG and DS scores was observed in the older adults groups. The SupraMG is a portion of the parietal lobe. Evidence from neuroimaging experiments suggests that the SupraMG is functionally involved in action execution, simulation, and observation (71). Previous rTMS studies have demonstrated that the SupraMG is functionally involved in visual word recognition (72), verbal working memory (73), and regulating egocentricity (74). In a recent study, the volume of the right SupraMG was found to be associated with the maintenance of emotion recognition ability (75). Combined with our findings, we believe that the right SupraMG plays an important role in the change of processing speed in older adults. The decrease of the gyrification index of the right SupraMG was correlated with the reduced processing speed of older adult females compared to males. Therefore, the right SupraMG can be used as an imaging marker of sexual cognitive differences between males and females in older adults.

### *Limitations*

There are several limitations to this study. First, this study used cross-sectional data. All data included in the present study were acquired from the DLBS data set, so we were unable to obtain further information, such as on body mass index, chronic diseases, lifestyles, and socioeconomic status (76), which are risk factors for impaired cognitive function in middle-aged and older adults. A multimodal investigation suggested diverse aspects of neurocognition were associated with obesity, particularly deficits in executive function and ineffective suppression of the default mode network (77). According to a recent cross-sectional study, more than 20 well-known and emerging diseases are associated with smaller brain volumes (78). Therefore, the influence of comorbidities, lifestyle, and socioeconomic status should be considered in future studies of brain aging and cognitive decline. In addition, the sample size in this study was not balanced between the four groups, which might have influenced our results. Therefore, it is unclear whether the results of this study will be consistent with other studies. Further validation is needed through evaluating more detailed clinical data and performing larger cross-sectional and longitudinal studies.

 

## Conclusions

The results of this study indicate that aging has a more significant impact on cognitive function alteration than does sex and that sex differences in cognitive function only appear in the older adult stage. The alterations of cortical morphology parameters had different correlations with age and sex. The alterations of cortical thickness were more sensitive to aging than were the other parameters. There were significant sex differences in the fractal dimension in middle-aged participants and the gyrification index in older adults. These parameters showed more significant differences in females than in males during the aging process, which might be related to the higher incidence rate of cognitive impairment in older females.

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## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-22-583/rc

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-22-583/coif). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).



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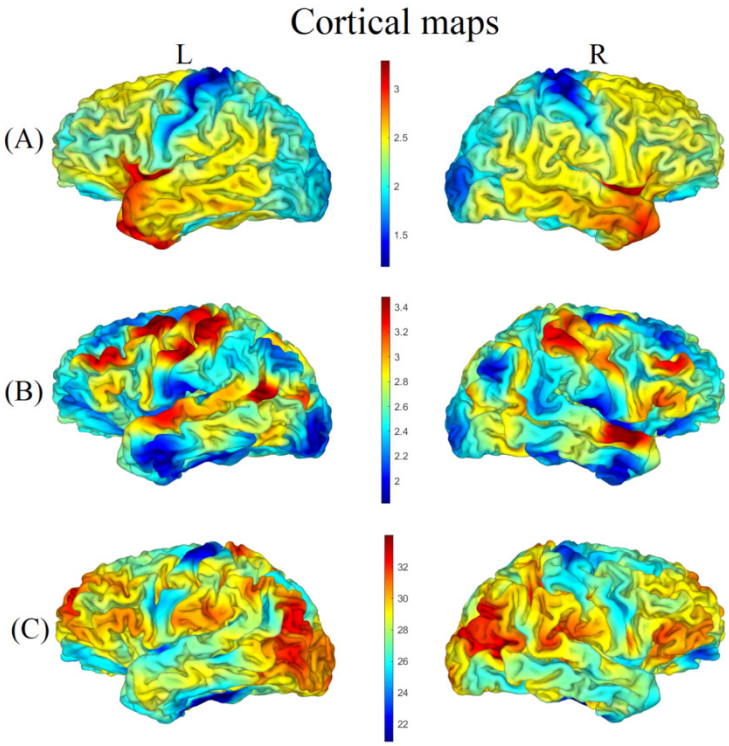


**Figure S1** Cortical maps of age-related distribution in individual participants. Lateral views of right (R) and left (L) hemispheres. (A) Cortical thickness maps (units: mm). (B) Fractal dimension maps (units: dimensionless). (C) Gyrification index maps (units: dimensionless).

**Table S1** Main age effect of cortical thickness

| Hemisphere | Overlap of atlas region | Cluster size (vertices) | Peak MNI coordinate | | | F value | P value (FWE) |
|---|---|---|---|---|---|---|---|
| | | | x | y | z | | |
| Left | 15% SFG; 8% PreCG; 8% PostCG; 8% SupraMG; 8% SPG; 7% rMFG; 6% PreCUN; 6% STG; 5% IPG; 4% cMFG; 3% LG; 3% pOPER; 3% ParaCG 3% LOG; 2% LFGor; 2% PCC; 2% pTRI; 2% INS; 1% FG; 1% PeriCAL; 1% CUN; 1% MTG; 1% TTG | 102,403 | –47 | –18 | –2 | 149.8 | <0.001*** |
| | 72% MTG; 28% bSTS | 1,017 | –64 | –41 | –7 | 31.3 | <0.001*** |
| | 90% Tpole; 5% MTG; 3% STG; 2% ITG | 584 | –28 | 14 | –38 | 29.8 | 0.001** |
| Right | 19% SFG; 8% SPG; 8% IPG; 7% rMFG; 7% PreCG; 7% PostCG; 7% SupraMG; 6% STG; 5% PreCUN; 4% MTG; 3% cMFG; 3% LOG; 3% ParaCG; 2% LG; 2% pOPER; 2% pTRI; 2% PCC; 1% FG; 1% LFGor; 1% bSTS; 1% INS; 1% CUN | 104,156 | 45 | –20 | –2 | 111.3 | <0.001*** |

**, P<0.01; ***, P<0.001. SFG, superior frontal gyrus; PreCG, precentral gyrus; PostCG, postcentral gyrus; SupraMG, supramarginal gyrus; SPG, superior parietal gyrus; rMFG, rostral middle frontal gyrus; PreCUN, precuneus; STG, superior temporal gyrus; IPG, inferior parietal gyrus; cMFG, caudal middle frontal gyrus; LG, lingual gyrus; pOPER, pars opercularis; ParaCG, paracentral gyrus; LOG, lateral occipital gyrus; LFGor, lateral orbitofrontal gyrus; PCC, posterior cingulate; pTRI, pars triangularis; INS, insula; FG, fusiform gyrus; PeriCAL, pericalcarine cortex; CUN, cuneus; MTG, middle temporal gyrus; TTG, transverse temporal gyrus; bSTS, banks of the superior temporal sulcus; Tpole, temporal pole; ITG, inferior temporal gyrus; MNI, Montreal Neurological Institute.


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**Table S2** Main age effect of the fractal dimension

| Hemisphere | Overlap of atlas region | Cluster size (vertices) | Peak MNI coordinate | | | F value | P value (FWE) |
|---|---|---|---|---|---|---|---|
| | | | x | y | z | | |
| Left | 82% PCC; 18% PreCUN | 1057 | –3 | –22 | 39 | 31.8 | <0.001*** |
| | 100% INS | 604 | –35 | 8 | 3 | 46.5 | <0.001*** |
| | 98% STG; 2% TTG | 486 | –54 | –5 | –2 | 30.6 | <0.001*** |
| | 77% LFGor; 23% INS | 239 | –29 | 16 | –24 | 24.2 | 0.007** |
| | 100% rMFG | 201 | –35 | 51 | 16 | 25.2 | 0.005** |
| | 84% MFGor; 16% RAC | 192 | –4 | 10 | –8 | 23.5 | 0.009** |
| | 100% pOPER | 172 | –45 | 11 | 24 | 25.7 | 0.004** |
| | 100% SFG | 139 | –10 | 66 | 12 | 20.9 | 0.027* |
| Right | 100% INS | 858 | 36 | 4 | 5 | 50.2 | <0.001*** |
| | 100% PreCUN | 244 | 16 | –63 | 30 | 25.9 | 0.003** |

*, P<0.05; **, P<0.01; ***, P<0.001. PCC, posterior cingulate; PreCUN, precuneus; STG, superior temporal gyrus; TTG, transverse temporal gyrus; LFGor, lateral orbitofrontal gyrus; INS, insula; rMFG, rostral middle frontal gyrus; MFGor, rostral middle frontal gyrus; RAC, rostral anterior cingulate; pOPER, pars opercularis; SFG, superior frontal gyrus; MNI, Montreal Neurological Institute.

**Table S3** Main sex effect of the fractal dimension

| Hemisphere | Overlap of atlas region | Cluster size (vertices) | Peak MNI coordinate | | | F value | P value (FWE) |
|---|---|---|---|---|---|---|---|
| | | | x | y | z | | |
| Right | 61% FG; 39% LG | 470 | 28 | –66 | –5 | 30.4 | 0.001** |
| | 100% LG | 210 | 5 | –66 | 4 | 22.8 | 0.009** |
| | 100% PreCUN | 198 | 56 | 9 | 30 | 23.6 | 0.011* |

*, P<0.05; **, P<0.01. FG, fusiform gyrus; LG, lingual gyrus; PreCUN, precuneus; MNI, Montreal Neurological Institute.

**Table S4** Main age effect of the gyrification index

| Hemisphere | Overlap of atlas region | Cluster size (vertices) | Peak MNI coordinate | | | F value | P value (FWE) |
|---|---|---|---|---|---|---|---|
| | | | x | y | z | | |
| Left | 56% INS; 17% STG; 9% SupraMG; 8% TTG; 6% pOPER; 2% PostCG; 2% pTRI | 5,427 | –33 | –30 | 16 | 49.2 | <0.001*** |
| | 100% IC | 213 | –5 | –50 | 14 | 22.8 | 0.012* |
| Right | 53% INS; 12% STG; 9% TTG; 9% PostCG; 6% pOPER; 6% SupraMG; 5% PreCG | 4,266 | 42 | –22 | –2 | 66.6 | <0.001*** |
| | 53% MFGor; 47% RAC | 769 | 34 | –21 | 46 | 39.7 | 0.001** |

*, P<0.05; **, P<0.01; ***, P<0.001. INS, insula; STG, superior temporal gyrus; SupraMG, supramarginal gyrus; TTG, transverse temporal gyrus; pOPER, pars opercularis; PostCG, postcentral gyrus; pTRI, pars triangularis; IC, isthmus cingulate; PreCG, precentral gyrus; MFGor, rostral middle frontal gyrus; RAC, rostral anterior cingulate; MNI, Montreal Neurological Institute.


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**Table S5** Main sex effect of the gyrification index

| Hemisphere | Overlap of atlas region | Cluster size (vertices) | Peak MNI coordinate | | | F value | P value (FWE) |
|---|---|---|---|---|---|---|---|
| | | | x | y | z | | |
| Left | 41% cMFG; 20% pOPER; 19% rMFG; 12% pTRI 5% pORB; 3% PreCG | 6109 | –55 | 18 | 20 | 40.1 | <0.001*** |
| | 91% LOG; 5% SPG; 4% IPG | 1420 | –40 | –81 | 7 | 30.5 | <0.001*** |
| | 96% SFG; 3% RAC; 1% CAR | 573 | –11 | 37 | 22 | 36.7 | <0.001*** |
| | 100% SPG | 390 | –17 | –78 | 45 | 25.0 | 0.005** |
| Right | 51% pOPER; 23% rMFG; 12% pTRI; 9% PreCG; 5% cMFG | 2412 | 40 | 13 | 23 | 39.6 | <0.001*** |
| | 52% SFG; 24% RAC; 13% MFGor; 11% CAR | 2266 | 13 | 36 | 16 | 46.4 | <0.001*** |
| | 62% cMFG; 38% rMFG | 2041 | 32 | 13 | 52 | 38.4 | <0.001*** |
| | 60% IPG; 27% LOG; 13% MTG | 839 | 45 | –66 | 6 | 30.6 | <0.001*** |
| | 100% LOG | 531 | 27 | –93 | 17 | 34.3 | <0.001*** |
| | 85% LFGor; 15% MFGor | 454 | 12 | 36 | –26 | 30.7 | <0.001*** |
| | 92% PostCG; 8% PreCG | 445 | 60 | –11 | 11 | 25.6 | 0.004** |
| | 100% rMFG | 370 | 35 | 52 | 7 | 25.8 | 0.003** |
| | 100% SupraMG | 188 | 63 | –41 | 23 | 23.6 | 0.018* |
| | 100% SFG | 147 | 22 | 12 | 60 | 23.3 | 0.010* |
| | 100% ITG | 132 | 50 | –46 | –18 | 21.9 | 0.017* |

*, P<0.05; **, P<0.01; ***, P<0.001. cMFG, caudal middle frontal gyrus; pOPER, pars opercularis; rMFG, rostral middle frontal gyrus; pTRI, pars triangularis; pORB, pars orbitalis; PreCG, precentral gyrus; LOG, lateral occipital gyrus; SPG, superior parietal gyrus; IPG, inferior parietal gyrus; SFG, superior frontal gyrus; RAC, rostral anterior cingulate; CAR, caudal anterior cingulate; MFGor, rostral middle frontal gyrus; MTG, middle temporal gyrus; LFGor, lateral orbitofrontal gyrus; PostCG, postcentral gyrus; SupraMG, supramarginal gyrus; ITG, inferior temporal gyrus; MNI, Montreal Neurological Institute.


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