Age-related gender-specific changes in the brain metabolism and morphology

Running title
Gender-specific changes in the aging brain

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Author contribution statement
Akihiro Kakimoto and Yasuomi Ouchi designed and performed the research, analyzed the data and wrote the paper. Shigeru Ito, Hiroyuki Okada and Sadahiko Nishizawa performed the research. Satoshi Minoshima supervised the project and advised the analysis.

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ABSTRACT

With a large database, we aimed to evaluate gender-specific distinctive changes of brain glucose metabolism and morphology during normal aging using Magnetic resonance imaging (MRI) and \textsuperscript{18}F-FDG positron emission tomography (PET).

Methods

A total of 963 cognitively healthy adults were included in this study. All subjects underwent medical questionnaire, mini mental state examination (MMSE) and whole-body examinations including brain MRI and whole-body \textsuperscript{18}F-FDG PET. We performed statistical analysis of the MR and PET images using three-dimensional stereotactic surface projection (3D-SSP). All images were corrected by whole brain pixel value to identify the brain regions with significant changes and regions of interest (ROI) were set up with reference to the Brodmann Area (BA). We evaluated morphological and glucose metabolic changes by the cross-sectional analysis. The baseline database consisted of the subjects from 30 to 40 years old and the age-step for comparison was each 5 years. We also compared gender-specific differences of MR and PET images in each generation.

Results

In age-related changes, the brain atrophy was observed in the lateral frontal and parietal regions, and the glucose hypometabolism was observed in the medial frontal regions in both genders. Between-gender comparison revealed significant sex differences in these parameters, showing that parallel changes in volume and metabolism were manifested in the medial frontal cortex in men and in the lateral and medial temporal cortex in women. By contrast, metabolism-dominant reductions were manifested in the lateral and medial parietal cortex in men and in the
ventrolateral prefrontal cortex, including the Broca area, in women. These differences became insignificant in individuals aged 66 years and older.

**Conclusion**

Our brain mapping study with a large number of normal human brain data demonstrates age-related, parallel changes between morphology and metabolism in the medial frontal regions, and gender-specific hypometabolism in the parietal (male) and the ventrolateral prefrontal (female) cortices. These findings may suggest a presence of aging vulnerability of gender-specific brain regions; the parietal cortex for the visuospatial ability in men and the Broca area for speech communication in women.

**Key words**

Brain atrophy, cognitive ageing, structural MR imaging, $^{18}$F-FDG PET and glucose metabolism
INTRODUCTION

The current trend of the increasingly number of dementia patients including Alzheimer’s disease (AD) (1) and the revised criteria for diagnosis of dementia by the National Institute on Aging and the Alzheimer’s Association (NIA-AA) (2-5), bring researchers to the greater attention of early detection of changes in the brain physiology during the preclinical stage. Indeed, the pathological changes of familial AD in the brain seem to develop 25 years before clinical symptom onset (6).

In order to detect preclinical stage of AD, it is necessary to catch a subtle abnormality that deviates from the healthy state. In other words, it is important to know the healthy brain morphology and activity beforehand. There are a number of researches that evaluated age-related changes and gender-specific differences in cognitively normal people using magnetic resonance imaging (MRI) or positron emission tomography (PET). To the best of our knowledge, however, findings from previous brain imaging studies support sex-specific differences in brain morphology and metabolism, just in conjunction with different psychological responses (7-10). Simple correlation analyses might have been difficult because of the limited number of samples. Therefore, in order to evaluate the details of age-related changes and subtle gender-specific differences in the brain morphology and glucose metabolism in each generation, we used large MRI and PET data of about 1,000 cognitively normal adults for that purpose.

MATERIALS AND METHODS

Subjects
The current study was approved by the Institutional Review Board of Hamamatsu Medical Photonics Foundation, and written informed consent was obtained from each participant after detail explanation of this study. A total of 963 cognitively normal, healthy adults ranging in age from 32 to 87 years were included in this study (493 male: 54.0±10.2 years; 470 female: 53.4±9.9 years) (Table 1). Medical interviews using psychological tests, blood testing and MRI verified that the subjects enrolled in this study were all cognitively normal and free from major illnesses. Several candidates were excluded because of incidentally identified cancer or brain abnormalities. The amounts of cigarette and alcohol use of the study individuals were within the range of habitual use in this population. As shown in Table 1, 10–20 % of participants received medicines that were prescribed orally but not intravenously or subcutaneously.

**MRI scan**

Magnetic resonance imaging was carried out using a 1.5-Tesla GE Signa Excite HD scanner (GE Healthcare). Three-dimensional structural MRI was acquired on each subject using a T1-weighted SPGR sequence (TR: 25 ms; TE: 6 ms; flip angle: 30°; NEX: 0.75; FOV: 24 cm; matrix size: 256×192; number of slices: 128; slice direction sagittal (AC-PC line was horizontal in the sagittal image); slice thickness: 1.5 mm).

**18F-FDG PET scan**

18F-FDG PET images were obtained using a high-resolution PET scanner (SHR-92000; Hamamatsu Photonics K.K., Hamamatsu, Japan) (11). All of the subjects fasted for at least 5 hours before the examination, and 3.0 MBq/kg 18F-FDG was injected thorough the cubital vein. After each subject rested in a dimly lit room for 50 minutes, the emission scan was performed for 15 minutes. The dynamic row-action maximum likelihood algorithm was employed for
image reconstruction. A CT scanner (GE Healthcare) was used for attenuation correction images (12). The matrix, pixel size, and slice thickness of the head area were $192 \times 192 \times 60$, $3.2 \times 3.2 \times 3.2$, and $3.2$ mm/pixel, respectively.

**Normalization of MR and PET images**

We performed the main statistical analysis of the MR and PET images using 3D-SSP (NEUROSTAT) (13). Regarding MR images, the MATLAB 7.8 program (R2009a, MathWorks INC.) and statistical parametric mapping (SPM8) were used for the realignment and segmentation of gray and white matter in MR images. After the segmentation by SPM, gray matter images of MRI were processed with spatial smoothing (9-mm FWHM) and 3D-SSP normalization. For the PET data, after spatial smoothing (9-mm FWHM) was performed, a normalization protocol of 3D-SSP was run. Next, the brain surface projection images of MRI and PET were obtained. Finally, all of the images were calculated by the correction of the whole brain pixel value to identify the brain regions where the degree of changes was large compared with the whole brain.

**Normal database**

As the baseline images for the brain surface projection, we created 4 types of database; MR database of male, MR database of female, PET database of male and PET database of female. As shown in Table 1, the male baseline database comprised 40 normal subjects aged 40 years and younger ($38.0 \pm 2.4$ years), and the female database comprised 33 normal subjects aged 40 years and younger ($38.1 \pm 2.0$ years). The minimal number of subjects in the year-based group was 23 in women aged greater than 70 years.

**Statistical analyses using 3D-SSP images**
We obtained the z-maps of all subjects by using a z-score protocol of 3D-SSP. For MR and PET images of the brain surface projection, we compared with male and female database, respectively. In the visual assessment of the brain morphology and glucose metabolism, the mean z-maps and gender-specific t-maps were used. For age-related changes, the mean z-maps classified by each 5-year range were made. For gender-specific differences, t-values relevant to both gender groups were calculated by t-test in every pixel of the brain surface projection images. In the generation of 3D-SSP images, the correction for multiple comparisons was used with the family-wise error rate (FWE) and the significance of t-value was defined as p < 0.05. The compared gender groups were set in each 5-year range.

**Brain regional analyses**

In the quantitative assessment of the brain morphology and glucose metabolism, we used the brain surface images performed the spatial normalization and the correction of the whole brain pixel value. Regions of interest (ROIs) were set up with reference to the Brodmann Area (BA) as described in detail elsewhere (Fig. 1) (14). For age-related changes, the mean pixel values of MR and PET in each BA were calculated for male and female, respectively. Pearson correlation coefficients (r) between age and mean values in BAs were calculated and transformed into t-values. For gender-specific differences, t-values relevant to both gender groups were calculated by t-test in every BA. The Bonferroni test was used for correction for multiple comparisons and the significance level was hence set as p < 0.05.

**RESULTS**

The age-based 3D-SSP analyses showed age-related similar changes (growing visibility of
atrophy and hypometabolism in individuals aged 46 years and older) in both sex groups (Fig. 2A and 2B). In these analyses, it the age-related brain atrophy (seen in red) was shown to extend laterally to the frontal, temporal, parietal and occipital lobes. In the medial side of the brain, the age-related glucose hypometabolism (seen in green) was observed dominantly in the prefrontal cortex (BA8, 9 and 10). In addition, the parallel declines in both brain atrophy and glucose hypometabolism (seen in yellow) were observed in the anterior cingulate gyrus (BA24 and 32). Between-gender comparison revealed significant sex differences in these parameters, showing that parallel changes in volume and metabolism (seen in yellow) were manifested in the medial frontal cortex (implicated functionally in error processing and performance monitoring (15); BA8, 9 and 24) in men and in the lateral and medial temporal cortex (functioned as emotional valence (16); BA20, 21, 22 and 38) in women (Fig. 3A and 3B). By contrast, metabolism reductions (seen in green) were manifested in the lateral and medial parietal cortex (subserving visuospatial sensory salience detection (17); BA5, 7 and 31) in men and in the ventrolateral prefrontal cortex, including the Broca area, (implicated functionally in predictive and integrative speech processing (18); BA44 and 46)) in women (Fig. 3A and 3B). These differences became insignificant in individuals aged 66 years and older.

Furthermore, in the brain regional analyses for testing the levels of changes quantitatively, we found similar changes seen in the voxel-based analysis as shown in Fig. 1 (Supplemental fig. 1 and 2). The Figure 4 was based on this analysis showing BAs where the significant gender-specific differences were seen. Men are shown to have smaller values in glucose metabolism in the medial parietal cortex (BA5, 7 and 31) and in brain volume in the medial frontal cortex (BA8, 9 and 24) than women (Fig. 4A and 4B). In contrast, glucose metabolism
in the lateral frontal cortex (BA44 and 46) and the brain volume in the lateral temporal cortex (BA20, 21, 22 and 38) were shown smaller in women than men (Fig. 4C and 4D).

**DISCUSSION**

We showed age-related reduction of gray matter volumes dominantly on the lateral sides (red color in Fig. 2A and 2B) as reported previously (19). Although there was no significant gender-specific difference in these affected areas, the progression and pattern of reduction were slightly different between genders. Interestingly, rapid decrease from 60 years of age was seen in men whereas gradual decrease from 40 years of age was seen in women. One possible explanation for this phenomenon is that it might be related to the sex hormone balance such as childbirth or menopause in the case of women and the life changes after resignation in the case of men. Since we have no data about hormone in this study, further study is needed to answer for this speculation.

In the results on the brain metabolic change by age, we found age-related glucose hypometabolism in the medial frontal region, which was consistent with the previous reports (10,20). Our intriguing finding, different from previous reports showing an age-related reduction in glucose metabolism seen roughly in the medial frontal region, was a difference in changes of metabolism and volume occurring within the medial frontal cortex. While glucose hypometabolism without brain atrophy was seen in the medial prefrontal cortex (green color in Fig. 2A and 2B), glucose hypometabolism with brain atrophy was seen in the anterior cingulate gyrus (yellow color in Fig. 2A and 2B). This suggests that the power or function per cell in the medial prefrontal cortex is more likely to decrease by age and that the neuronal loss
in the gray matter of the anterior cingulate gyrus is characteristic of age-related phenomenon.

Regarding the sex difference in the metabolic and morphological changes, the findings are, in part, not compatible with the previous findings \((9,10)\) possibly because a mixture of people with a large age range would obscure the difference in the statistical comparison. As shown in the present findings concerning sex differences in brain morphology and metabolism (red and green color in Fig. 3A and 3B), age-matched comparison in each age range may be important in the evaluation of gender-specific differences. In this comparison, as reported in many studies, the frontal cortex and periventricular regions in men are shown to be more atrophic than in women possibly due to a higher frequency of alcoholic intake in men \((21)\). In fact, according to the interview sheets of all participants in this study, men \((66.7\%)\) drank more alcohol than women \((24.0\%)\) in their daily lives. Therefore, the morphological changes between genders may not be a reflection of innate development but of external factors.

In contrast to MRI findings, there are interesting changes in glucose metabolism. As shown in Figure 4, reductions in glucose metabolism in men and women in the subtraction analyses were observed in the medial parietal cortex \((BA5, 7 \text{ and } 31)\) and lateral frontal cortex \((BA44 \text{ and } 46)\), respectively. The glucose hypometabolism in men corresponded to a visuospatial sensor \((17,22,23)\), while that in women corresponded to a integrative speech processing region including the Broca area \((18)\) and a complex sentence processing region \((24)\). Although the age-related metabolic changes were apparent, and the sex difference was manifest during adulthood, the difference became smaller as age advanced in the present study. As shown in Figure 4, gender-different reductions in metabolism are only present in the male parietal and female ventrolateral prefrontal cortices, which might make their behaviors gender-specific.
until neuronal attrition causes them to become similar with age (Fig. 3A and 3B). Because the explanation for this gender difference needs to be explored, a further study on age-related changes in brain activation during the gender-specific behaviors is necessary.

In the present study, we demonstrated the gender-characteristic metabolic changes measured under the resting state. As shown in many activation studies, women in adolescence (25) are more efficient than men in tasks of selective attention, verbal fluency, reasoning and speech reading, whereas men outperform women in tasks of visuospatial processing and mental rotation (26-29). Interestingly, the present finding on gender difference in the resting state metabolism study seems very similar to the results from those activation studies on gender differences. Therefore, such gender-specific differences may be present even on the resting state cellular level.

Considering the concept of cognitive reserve in healthy people—i.e., professional people may have functional specialization or energy-saving utilization in the brain in contrast to nonprofessionals (30,31) and the performance in a verbal task in healthy adults may correlate negatively with the degree of regional glucose metabolism at rest (32,33), it can be assumed that acquired low (efficient) energy consumption in gender-specific brain regions might have been depicted from the present precisely-classified between-gender subtraction analysis. Indeed, it is often said that men outperform women in task of visuospatial processing and women outperform men in speech processing (26-29). These gender-specific phenomena seen in daily lives need to be explored with a scientific approach.

There are several limitations in the present study. First, we analyzed only resting-state metabolic images. A future study is needed to verify whether greater reduction in metabolism
at rest can follow greater activation during specific tasks in individuals with special cognitive ability. Second, a lack of detailed examination for neuropsychological functions in each participant did not allow the comparison of the cognition behavior valence with the degree of brain metabolism at rest. Third, this study was not designed to follow individuals in a longitudinal fashion but to make cross-sectional assessments. Fourth, the partial volume effect existed in this study. Especially, small areas might be affected by partial volume effect and 3D-SSP misregistration. Therefore, the pixel counts of PET might be subject to the influence of the subject’s brain morphology. The correction using MRI data may reduce the partial volume effect.

CONCLUSION

With 963 normal human brain data, we demonstrated the age-related parallel changes between morphology and metabolism in the medial frontal regions and the gender-specific hypometabolism in the parietal (male) and the ventrolateral (female) cortices. These findings may partly answer for the well-accepted phenomenological question “why men don’t listen and women can’t read maps.” To confirm this, it is necessary to demonstrate sex-difference activations in these regions during gender-specific tasks.

ACKNOWLEDGEMENTS

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Figure 1.

Brodmann area (BA) on 3D-SSP template images based on a previous report (14). Each BA was segmented on the brain surface projection atlas (MRI template) of the 3D-SSP tools. In this report, the right/left hemispheres and lateral/medial cortices were distinguished and analyzed individually. The figures denote the left lateral (A) and right medial (B) brain regions.
Figure 2.

Age-related changes in the 3D-SSP z-score of male (A) and female (B) in different age groups of 5-year increments. The male and female database comprised 40 and 33 subjects at age 30-40 (described in “Normal database” section of MATERIAL AND METHODS). The red and green colors indicate reductions in the levels of MRI and PET values, respectively. The yellow color denotes a mixture of MRI (red) and PET (green) values, indicating a parallel change.
Figure 3.

Age-related changes t-map images of male < female (A) and female < male (B) in different age groups of 5-year increments. The red and green colors indicate reductions in the levels of MRI and PET values, respectively. The yellow color denotes a mixture of MRI (red) and PET (green) values, indicating a parallel change.
Figure 4.

Brodmann area (BA)-based analysis between genders. The vertical axes show the pixel value by the correction of the whole brain count. Asterisks tagged on PET denote dominant changes in metabolism, as seen in A and C. The presence of both asterisks (MRI and PET) denotes parallel changes in morphology and metabolism, as seen in B and D. The inset pictures indicate BAs of interest.

n.s. non significant, *: p<0.05.
Table 1. Subject demographics

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<th>Age in years</th>
<th>Male (M)</th>
<th>Female (F)</th>
<th>Comorbid diseases</th>
<th>Others</th>
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<td>470</td>
<td>29.5±0.7</td>
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