Clinical Investigative Study

Sex- and Age-Related Differences in Brain FDG Metabolism of Healthy Adults: An SPM Analysis

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ABSTRACT

BACKGROUND AND PURPOSE

The purpose of our study was aimed to analyze the sex- and age-related differences of brain metabolism in healthy individuals.

METHODS

Consecutive 100 healthy subjects, 50 males and 50 females, undergoing routine 2-[^{18}F]-fluoro-2-deoxy-d-glucose positron emission tomography (FDG PET) for health checkup in our hospital were retrospectively enrolled in this study. Statistical parametric mapping (SPM) was used for analyses of the FDG PET images to disclose the possible effects of age on brain metabolism in males and females as well as the differences of brain metabolism between male and female groups.

RESULTS

In males and females, decreased brain metabolism with aging is found in bilateral lateral orbital prefrontal and right anterior cingulate cortices. In comparisons between sexes, males are found to have more brain metabolism than females in bilateral visual cortices and cerebellum.

CONCLUSIONS

Our report discloses different sex- and age-related brain metabolism. Decreased brain metabolism with aging in males and females is similar to findings reported in previous literatures. However, whether declined brain function or volume with aging causing metabolic changes is unknown and should be further evaluated. Nevertheless, the sex-related differences are possibly compatible with the historical observation of better performance in visual-spatial tasks in males than females.

Keyword: 2-[^{18}F]-fluoro-2-deoxy-d-glucose positron emission tomography, brain metabolism, statistical parametric mapping, sex, age, healthy adult.

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Introduction

Differences of brain metabolism of 2-[^{18}F]-fluoro-2-deoxy-d-glucose (FDG) had been found in many patients with neurodegenerative and psychiatric disorders.[1-19] In contrast to the rapid development of the diseased spectrum of altered brain metabolism of FDG, much fewer studies focused on the sex- or age-related influences of different brain metabolism in healthy individuals and many of them were subgroups as normal control subjects in comparison with various diseased patients.[1,3,5,9,12,20-32] Nevertheless, the analytic results of normal subjects were also greatly divergent. Our current retrospective study was specifically aimed to analyze the potential differences between groups of healthy subjects with different ages and sexes, and tried to discuss the possible explanations for the sex- or age-related differences if existed.

Materials and Methods

Subjects

From July 2002 to December 2003, consecutive 528 examinees underwent a routine FDG positron emission tomography (FDG PET) in our hospital. In these examinees, a total of 100 subjects who underwent FDG PET for routine health checkup and were consisted of 50 males and 50 females were retrospectively enrolled for analysis in this study. All of the enrolled subjects did not have known neurodegenerative disorders, psychiatric diseases, previous cerebral vascular accident, head trauma, or use of neuropsychological medication. Because of their initial demands of FDG PET were routine health checkup, the whole-body scans for screening occult malignancies were also reviewed and none of them had such findings.

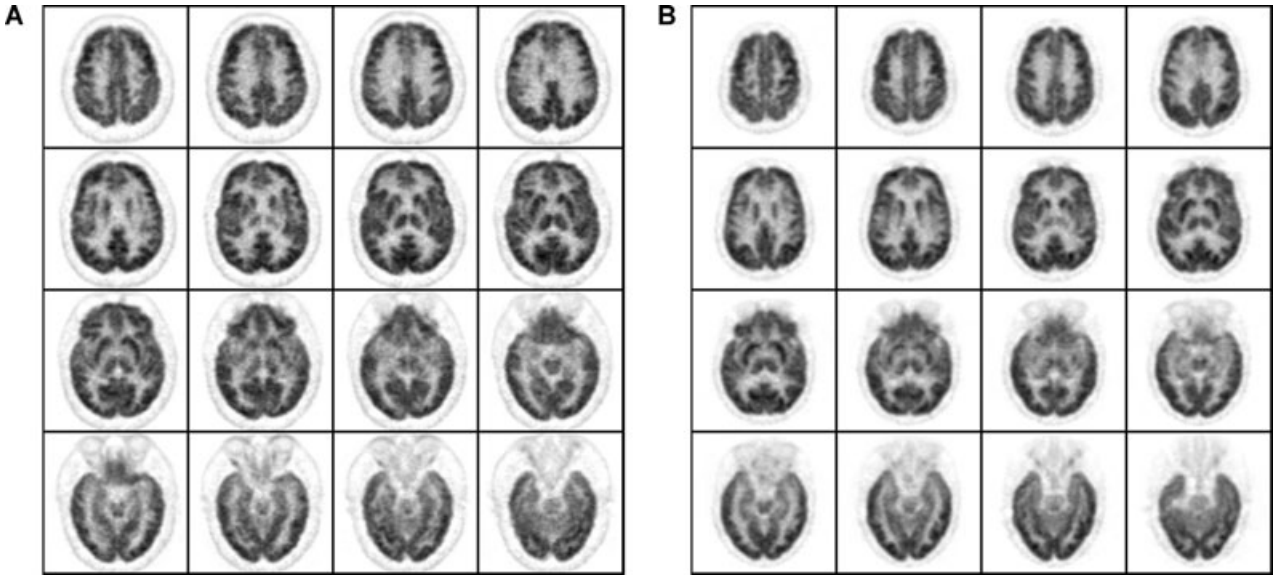

Fig 1. FDG PET images of the healthy male's and female's brains. The panel A shows a representative transaxial slice of a 58-year-old male's brain and panel B shows a representative transaxial slice of a 58-year-old female's brain.

FDG PET

All subjects were asked to fast at least 4 hours before scanning. Each of them was injected intravenously with 370 megabecquerel (MBq) of FDG and rested supine with their eyes closed in a quiet, dimly lit room. Imaging was performed with a positron emission tomography scanner (General Electric Advance Nxi, General Electric Medical Systems, Milwaukee, WI, USA). Scanning began 40 minutes after injection of FDG. When subjects were positioned in the scanner, a molded headrest and a head-restraining Velcro band were applied to firmly secure their heads in order to reduce motion artifact. Whole-body PET images were acquired from the head to upper thighs in the 2-dimensional mode. Three-minute emission scan and 1-minute transmission scan, using ^{68}Ge pin sources, were acquired per bed position (axial field of view: 15 cm) and reconstructed onto 35 axial image slices (slice width: 4.25 mL). After finishing the whole-body scan, the brain scan commenced by 18-minute 3-dimensional emission scan ensued by a 3-minute 2-dimensional transmission scan. Thirty-five slices at 4.25-mm intervals were obtained to cover the whole brain. Images were reconstructed by Fourier rebinning ordered subsets expectation maximization (FORE-OSEM) algorithm into $128 \times 128 \times 35$ image matrices (voxel size: $1.95 \times 1.95 \times 4.25$ mm^3), using segmented attenuation correction (Fig 1).

Statistical Analysis

A voxel-by-voxel group analysis was done using SPM99 (Welcome Department of Cognitive Neurology, University College, London) running on MATLAB (version 6.0; MathWorks Inc., Natick, MA, USA) to compare the difference of regional brain glucose metabolism between different groups of healthy individuals described above. Statistical parametric mapping (SPM) is a statistical method used for image analyses and can automatically determine statistical differences between sets of images obtained between different experimental conditions or between sets of images obtained from different groups of subjects. Its most common application is to assess significant changes in regional brain activity. The method is based on the averaging of images across groups of subjects distinguished on the basis of biologic variables, disease processes and/or activation conditions. This is accomplished with a series of steps, involving a linear spatial registration (spatial realignment), a nonlinear spatial registration (plastic transformation), an anatomic normalization to reference space (Talairach and Tournoux Atlas), a linear global functional normalization and the computation of statistical significance parameters (such as T-statistics in our study). The parameters of computed statistical results presented in our study include those sets of volume clusters (k) with statistical significant voxel height (T) and their representative coordinates (x, y, z) of the Talairach and Tournoux Atlas with highest voxel height within the individual clusters.

The FDG PET images were initially converted from the DICOM to the ANALYZE format using MRIcro (available at www.mricro.com), and transferred to SPM99. MRIcro allows efficient viewing and creating analyze format headers for exporting brain images to other platforms with common personal computers. After transferring to SPM99, the data were then normalized into standard PET template provided in SPM99 by using a 12-parameter affine transformation, followed by nonlinear transformations and bilinear interpolation. Dimensions of the resulting voxels were $2 \times 2 \times 2$ mm^3. Standardized data were then smoothed by a Gaussian filter (full width of half maximum, FWHM = 16 mm). Male and female subjects were analyzed, respectively, with their ages as the covariance to check the relationship between the age and brain metabolism. In addition, male subjects were compared with female subjects with age as the nuisance variable to analyze the sex-related differences in brain metabolism. Normalization of global FDG metabolism was performed using proportional scaling to a mean brain blood

Table 1. Descriptive Statistics of the Subjects in This Study

Sex	Number	Age (Years Old) Mean ± Standard Deviation	95% Confidence Interval	*P* value†
Male	50	58.58 ± 12.00	56.88~60.29	0.68
Female	50	57.56 ± 11.17	55.97~59.15	

†Two sample t test.

flow of 50 mL per 100 g per minute and an analysis threshold masking by 100% of mean brain blood flow. The statistical parametric map SPM was initially obtained at a height threshold T to meet $P = .05$ (corrected with familywise error), and then an extent threshold k was set as 100 voxels. The Talairach Daemon database was used to convert the coordinates of these statistical significant areas into correspondent anatomical locations in the Talairach and Tournoux atlas. Results were listed with the Talairach coordinates of the representative peak voxels, as well as their individual k value, t score, and Brodmann area (BA). The k value represents the number of significant voxels in the particular cluster.

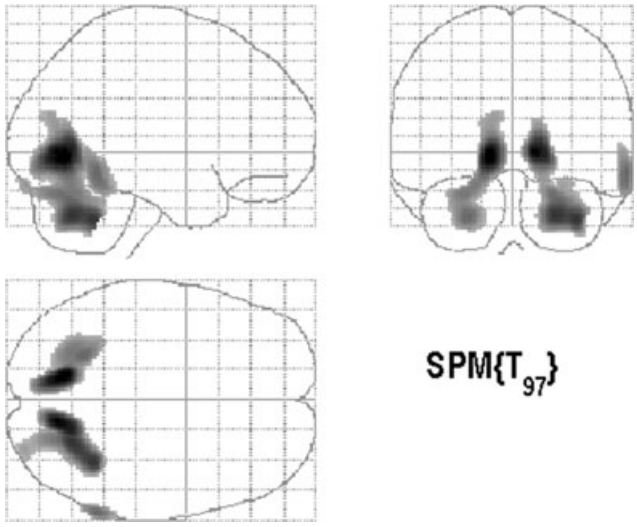

Fig 2. Differences of brain metabolism between males and females on the 3-orthogonal maximum intensity projection glass brain graphic displays of SPM99. Only clusters representing relative hypermetabolism in males survive.

Results

Subject Characteristics (Table 1)

The average age of male and female subjects was 58.58 ± 12.00 and 57.56 ± 11.17 years old, respectively. There was no statistic difference between ages in different sex groups ($P = .68$).

SPM Analyses

Comparison of the Sex-Related Difference in Brain Metabolism (Table 2)

There are three clusters of relative brain hypermetabolism in male subjects (Fig 2). The most prominent two clusters (>1,500 voxels) are in a symmetrical pattern locating in bilateral visual cortices and cerebellar hemispheres. The other small cluster (157 voxels) is located in the right temporal lobe. On the other hand, there is no suprathreshold cluster (≥100 voxels) representing areas with relative brain hypermetabolism in female subjects in this analysis.

Analysis of the Effect of Age on Brain Metabolism in Male Subjects (Table 3)

Focalized small areas representing relatively decreased brain metabolism, while the age increases are noted in bilateral lateral orbital prefrontal cortex and right ventral anterior cingulate cortex (Fig 3). On the other hand, there is no suprathreshold cluster representing areas with relatively increased brain metabolism, while the age increases in males.

Analysis of the Effect of Age on Brain Metabolism in Female Subjects (Table 4)

Several areas, mainly the subcortical ones, are noted with relatively increased brain metabolism, while the age increases (Fig 4A). On the other hand, areas representing relatively decreased brain metabolism, while the age increases are noted in bilateral lateral orbital prefrontal cortices and right dorsal anterior cingulate cortex in females (Fig 4B).

Discussions

With the advent of many new neuroimaging modalities in past decades, many investigators have been tried to find if there is any accountably anatomical or functional change of the brain that is able to explain the variety of human neurological, psychiatric, and behavioral manifestations. Many clinical conditions, especially the neurodegenerative diseases, psychiatric disease, and drug effects, have been extensively surveyed with these neuroimaging modalities but quite a lot of them remain

Table 2. SPM Results of Sex-Related Differences of Brain Metabolism†

Comparison	Cluster	k	T	Talairach Coordinates x	y	z	Anatomical Location	Brodmann Area
Relative hypermetabolism in males than females‡	1	1534	6.98	−14	−68	−4	Left secondary visual cortex	18
			5.60	−24	−58	−36	Left cerebellum	
	2	1718	6.83	12	−73	0	Right secondary visual cortex	18
			6.29	24	−64	−36	Right cerebellum	
	3	157	5.59	64	−50	−12	Right inferior temporal gyrus	20

†No suprathreshold clusters of relative female-to-male hypermetabolism.
‡Voxel height threshold T = 4.58; $P = 0.05$ with familywise error correction; cluster extent threshold k = 100 voxels.

Table 3. SPM Results of Age-Related Differences of Brain Metabolism in Male Subjects[†]

Comparison	Cluster	k	T	Talairach Coordinates x	y	z	Anatomical Location	Brodmann Area
Relatively decreased metabolism in males with aging[‡]	1	254	6.47	38	18	−16	Right lateral orbital prefrontal cortex	47
	2	315	6.38	2	24	22	Right ventral anterior cingulate cortex	38
	3	141	5.76	−36	20	−14	Left lateral orbital prefrontal cortex	47

[†]No suprathreshold clusters of relatively increased metabolism with aging.
[‡]Voxel height threshold T = 5.01; $P = 0.05$ with familywise error correction; cluster extent threshold k = 100 voxels.

inconclusive because of their divergent neuroimaging presentations. On the other hand, much fewer studies have tried to find the differences of brain functions among the normal healthy subjects despite the apparent differences of individuals' personality, behavior, or emotion that was intuitively thought to be related to the differences of receiving, processing, and executive functions of brain. However, the recently explosive improvement of research tools including the magnetic resonance imaging (MRI), PET, and graphic statistical analytic software such as SPM has brought out the much better understanding of the brain functions. Compared with the great interest in searching for the difference of structural or anatomical differences of normal human brains,[33-40] less research has been conducted focusing on brain metabolism and resting brain functions of the normal healthy individuals evaluated with PET.[25,31] Perhaps, the potential cause of this preference is the concern about the ionizing radiation. Until now, there are still two mysteries about the human brain that always confuse us: "How does the human brain grows old?" and "Which differences in the brain make men act so different from women?" Previously published literature has shown that brain volume is greater in men than women, with a higher percentage of gray matter in women and a higher percentage of white matter in men.[34] The earlier voxel-based morphometric studies reveal the volume of gray matter decreasing with age but do not show significant sex-related differences.[35,36] However, a recent voxel-based morphometric study does show both age and sex are related to the differences in human brain volume.[37] Reported regional differences between male and female brains are divergent among literatures but most consistently founded in the basal ganglia, hippocampus, and amygdala.[39] As for the age-related voxel-based morphometric change, gray matter volume loss is mainly in bilateral frontal lobes, including dorsolateral prefrontal cortex, sensorimotor areas, and orbitofrontal regions.[23,41]

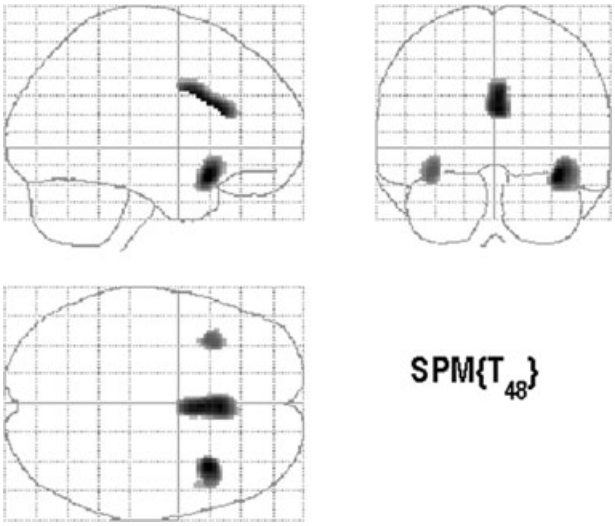

Fig 3. Changes of male brain metabolism with aging on the 3-orthogonal maximum intensity projection glass brain graphic displays of SPM99. There are only areas revealing decreased metabolism with aging in this analysis.

The functional images using single photon emission computed tomography (SPECT) or PET also show a wide variety of the age- and sex-related differences surrounding brain function. Some previous studies did not find any difference of brain functional images between males and females.[5,21,24,28] A study reported the whole-brain glucose metabolic rates were 19% higher in females than those in the males, but the authors concluded that the findings might be the effect of estrogen.[27] Age-related changes in brain metabolism were also observed in most studies. However, some of these studies reported brain regions showing decreased metabolism with aging only[1,9,12,22,23,26,32] but some reported not only decreased but also increased metabolism in several brain regions.[20,29-31] Rather, some authors have advocated that those brain regions demonstrating increased metabolism with aging should be interpreted with caution since these findings may be artifacts owing to imperfect methodological assumptions of "global mean normalization" of the brain glucose metabolism.[42-45] Nevertheless, increasingly recent studies of healthy subjects have shown significant differences of brain metabolism between men and women[3,25,31] as those sex-related differences demonstrated in various neuropsychological conditions and diseases.[2-6,13,15,19]

Our analyses use the method of "global mean normalization" of the brain glucose metabolism that may cause analytical results of artifactual brain hypermetabolism with aging as mentioned earlier. To reduce this drawback, we have elevated the analytical threshold of the normalizing factor (100% rather than preset 80%) and used a more rigorous method of statistical correction (correction of familywise error). Despite these modifications, we still observe hypermetabolic brain regions, mainly the subcortical regions, with aging in female subjects, which are characteristic findings of artifactual brain hypermetabolism with aging using global mean normalization.[43] These findings should be interpreted with caution and not simply be regarded as true aging changes. On the other hand, both males and females show similar hypometabolic regions with

Table 4. SPM Results of Age-Related Differences of Brain Metabolism in Female subjects

Comparison	Cluster	k	T	Talairach Coordinates x	y	z	Anatomical Location	Brodmann Area
Relatively increased metabolism in females with aging[†]	1	687	7.53	−16	−14	−4	Left thalamus	
	2	655	7.49	18	−10	−2	Right thalamus	
	3	150	6.85	−28	8	14	Right putamen	
	4	297	6.79	−20	−64	−48	Left cerebellum	
	5	149	6.13	−12	−26	60	Left premotor cortex	4
	6	122	5.60	20	−66	−46	Right cerebellum	
Relatively decreased metabolism in females with aging[†]	1	442	7.57	−38	20	−14	Left lateral orbital prefrontal cortex	47
	2	328	6.85	42	18	−18	Right lateral orbital prefrontal cortex	47
	3	119	5.71	2	36	22	Right dorsal anterior cingulate cortex	32

[†]Voxel height threshold T = 4.97; $P = 0.05$ with familywise error correction; cluster extent threshold k = 100 voxels.

aging in bilateral lateral orbital prefrontal cortices and anterior cingulate cortex. These hypometabolic regions are in accordance with those that have been reported previously.[31] However, decreased brain volume is also present in these similar regions in some morphometric studies.[23,41] Thus, whether decreased brain metabolism is totally or partly caused by decreased brain volume may need further validation with correction of partial volume effects.[46,47]

In addition, the sex-related differences of brain metabolism reveal relative hypermetabolism in bilateral visual cortices and cerebellum in male subjects. The previous studies have recognized that males perform better in the visual-spatial domain, whereas females perform better in the verbal domain of cognitive tasks.[48,49] A more recent functional MRI (fMRI) study also provide evidences of more prominent brain activation in the occipital cortex in males during visual-spatial cognitive tasks.[50] Another recent voxel-based morphometric study also shows relatively retained gray matter with aging in older males.[37] These studies along with our study show the consistency of the male predominance, whether in morphology, activating function or resting function, in the occipital lobe, which account for the better performance in visual-spatial tasks in males. Moreover, males also have relative brain hypermetabolism in bilateral cerebellar regions. Although the earlier studies have been reported the similar male predominance in morphology[33] and function,[51] there is still no consistent explanation for this difference, whether it suggests the differential manifestations in attention, emotion or motor control.

There are several limitations of our study. The major limitation is the retrospective design. Therefore, certain factors, such as handedness, menstruation, education, occupation, etc, that are assumed capable of influencing the regional brain functions cannot be obtained or eliminated. Second, in order to reduce results of artifactual brain hypermetabolism with aging because of the normalization method of global FDG metabolism, we use more strict analytical threshold and rigorous correction method in SPM that may decrease the sensitivity of discovering the sex- and age-related differences in our study. Third, we do not apply a volume-correction method to compensate the relative inferior spatial resolution of PET to morphological image template. Therefore, we cannot differentiate if the hypometabolic regions are the result of decreased brain parenchyma or actually decreased function in addition to the volume loss. Future studies are advocated with the proper normalization and volume corrections method to avoid these limitations.

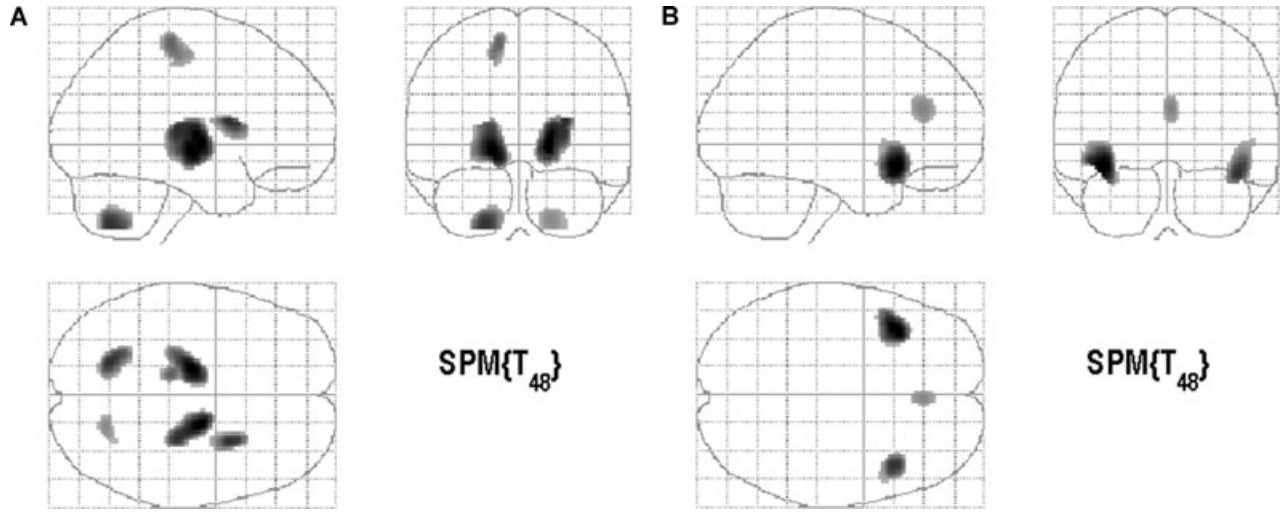

Fig 4. Changes of female brain metabolism with aging on the 3-orthogonal maximum intensity projection glass brain graphic displays of SPM99. The panel A shows areas of increased metabolism with aging and panel B shows areas of decreased metabolism with aging.

Conclusions

Our study discloses similar decreased brain metabolism with aging in bilateral lateral orbital prefrontal cortices and anterior cingulate cortex in both males and females. Nevertheless, there are sex-related differences with relative hypermetabolism in bilateral visual cortices and cerebellum in males. The differential metabolism in the visual cortex is in accordance with the findings in previous behavioral, morphometric, and functional studies, suggesting the relationship of male predominant visual-spatial cognitive function. However, it remains unclear how the sex-related differential metabolism in the cerebellum influences the behavior or cognition between males and females.

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