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Cortical Thickness and Brain Glucose Metabolism in Healthy Aging

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Background and Purpose We aimed to determine the effect of demographic factors on cortical thickness and brain glucose metabolism in healthy aging subjects.

Methods The following tests were performed on 71 subjects with normal cognition: neurological examination, 3-tesla magnetic resonance imaging, ^{18}F-fluorodeoxyglucose positron-emission tomography, and neuropsychological tests. Cortical thickness and brain metabolism were measured using vertex- and voxelwise analyses, respectively. General linear models (GLMs) were used to determine the effects of age, sex, and education on cortical thickness and brain glucose metabolism. The effects of mean lobar cortical thickness and mean lobar metabolism on neuropsychological test scores were evaluated using GLMs after controlling for age, sex, and education. The intracranial volume (ICV) was further included as a predictor or covariate for the cortical thickness analyses.

Results Age was negatively correlated with the mean cortical thickness in all lobes (frontal and parietal lobes, p=0.001; temporal and occipital lobes, p<0.001) and with the mean temporal metabolism (p=0.005). Education was not associated with cortical thickness or brain metabolism in any lobe. Male subjects had a lower mean parietal metabolism than did female subjects (p<0.001), while their mean cortical thicknesses were comparable. ICV was positively correlated with mean cortical thickness in the frontal (p=0.016), temporal (p=0.009), and occipital (p=0.007) lobes. The mean lobar cortical thickness was not associated with cognition scores, while the mean temporal metabolism was positively correlated with verbal memory test scores.

Conclusions Age and sex affect cortical thickness and brain glucose metabolism in different ways. Demographic factors must therefore be considered in analyses of cortical thickness and brain metabolism.

Keywords MRI; cortical thickness; FDG; brain glucose metabolism; healthy aging.

INTRODUCTION

Cortical atrophy in MRI is a useful imaging biomarker for detecting and monitoring several dementia diseases, including Alzheimer's disease (AD), dementia with Lewy bodies (DLB), and vascular dementia.[1,2] Advances in neuroimaging techniques, especially in PET using specific tracers for β-amyloid and dopamine transporter (DAT), made accurate in vivo diagnoses of AD and DLB possible.[3-5] Characteristic patterns of cerebral glucose metabolism on ^{18}F-fluorodeoxyglucose (FDG) PET are also useful for the differential diagnosis of neurodegenerative diseases.[6,7]

Reliable methods have been developed for quantitatively measuring brain atrophy and metabolism. However, the confounding effects of demographic factors such as aging and sex need to be considered in studies on dementia diseases, since these factors affect brain atrophy and metabolism. The effect of age on cortical atrophy has varied among neuroim-

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aging studies; aging was found to be related to widespread cortical thinning[8,9] or to thinning in some parts of the brain such as the anterior frontal and temporal lobes,[10] or the occipital and temporal lobes.[11] A sex effect has not been consistently found in previous studies, with females found to have thicker cortexes than males[11-13] or vice versa.[10] The effect of education has also been inconclusive.[10,11]

Neuroimaging studies related to brain metabolism have found inconsistent results for the effects of demographic factors. Age-related hypometabolism was relatively localized in several brain areas compared with cortical thinning. Higher age was related to decreased metabolism in the anterior brain, but there has been inconsistency regarding the specific cortical region.[8,9,14,15] The sex effect differed among studies, with female participants having higher overall cerebral glucose metabolism than male participants,[15] and the regions with high brain metabolism differing between the sexes.[8] Few studies have investigated the effects of education on brain metabolism.[15,16]

These inconsistent results might be attributable to differences in study populations and comorbid neuropathologies. We are not aware of any database that contains extensive MRI and FDG-PET data collected from subjects with normal cognition. We therefore collected structural MRI and FDG-PET data on subjects with normal cognition who underwent β-amyloid PET and DAT-PET in order to exclude underlying neurodegenerative changes. We evaluated the effects of demographic factors including age, sex, and education on cortical thickness by using structural MRI and on brain glucose metabolism by using FDG-PET, and their relationships with cognition scores. We hypothesized that demographic factors, especially age, significantly affect brain atrophy and glucose metabolism.

METHODS

Participants

This study initially included 141 subjects who did not have subjective cognitive dysfunction. The inclusion criteria of this study were 1) age >50 years and 2) no objective cognitive dysfunction in the detailed neuropsychological test as described below. The exclusion criteria were 1) score on the Korean version of the Mini-Mental State Examination (K-MMSE) of <26; 2) difficulty in participating in coordinating interviews and self-administered surveys (literacy, hearing impairment, and speech impairment); 3) previous history of neurological or psychiatric disorders such as territorial cerebral infarction, severe head trauma, brain surgery, intracranial hematoma with permanent brain lesion, major affective disorder, schizophrenia, or schizoaffective disorder; 4) contraindication to MRI; or 5) underwent radiation therapy or radiation exposure tests in another clinical study. Among the 141 subjects, 57 were excluded, comprising 2 subjects who had abnormal K-MMSE scores, 43 who had abnormalities in the neuropsychological test, and 12 who had abnormalities in brain MRI. Further evaluations were finally performed on 84 subjects (37 males and 47 females), which consisted of PET scans for β-amyloid deposition, DAT uptake, and glucose metabolism for the subjects that used ^{18}F-florbetaben (FBB) PET, ^{18}F-N-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl) nortropane (FP-CIT) PET, and FDG-PET. FBB-PET was applied to 32 of the 37 male subjects, which revealed 2 (6.3%) who were amyloid positive, and to 33 of the 47 female subjects, which revealed 2 (6.1%) who were amyloid positive. FP-CIT-PET scans were performed on 26 male and 30 female subjects, and 1 female (3.3%) had decreased striatal DAT uptake. All male subjects and 38 of the 47 female subjects received FDG-PET. Participants who had abnormal PET findings or did not receive FDG-PET were excluded. Finally, 71 participants were included for further analysis (Supplementary Fig. 1 in the online-only Data Supplement).

Standard protocol approval, registration, and patient consent

This study was approved by the Institutional Review Board of Yonsei University College of Medicine (No. 4-2015-0551). Informed consent was obtained from all participants.

Neuropsychological tests

All participants underwent the Seoul Neuropsychological Screening Battery[17] and standardized z scores based on age- and education-matched norms were available for attention, language, visuospatial function, memory, and frontal/executive function. We included the digit-span backward test for the attention domain; the Korean version of the Boston Naming Test for the language domain; copying item of the Rey–Osterrieth Complex Figure (RCFT) test for the visuospatial domain; immediate recall, 20-minute delayed recall, and recognition items of the RCFT and Seoul Verbal Learning Test (SVLT) for the memory domain; and the semantic Controlled Oral Word Association Test (COWAT), phonemic COWAT and the Stroop color reading test for the frontal/executive domain. The K-MMSE was used to assess global cognitive performance.

Image acquisition and interpretation

All MRI scans were acquired using a 3.0-tesla scanner (Philips Intera, Philips Medical System, Best, the Netherlands) using a previously described protocol.[2] The head of each subject was firmly fixed during the scan using foam padding, neck cush-

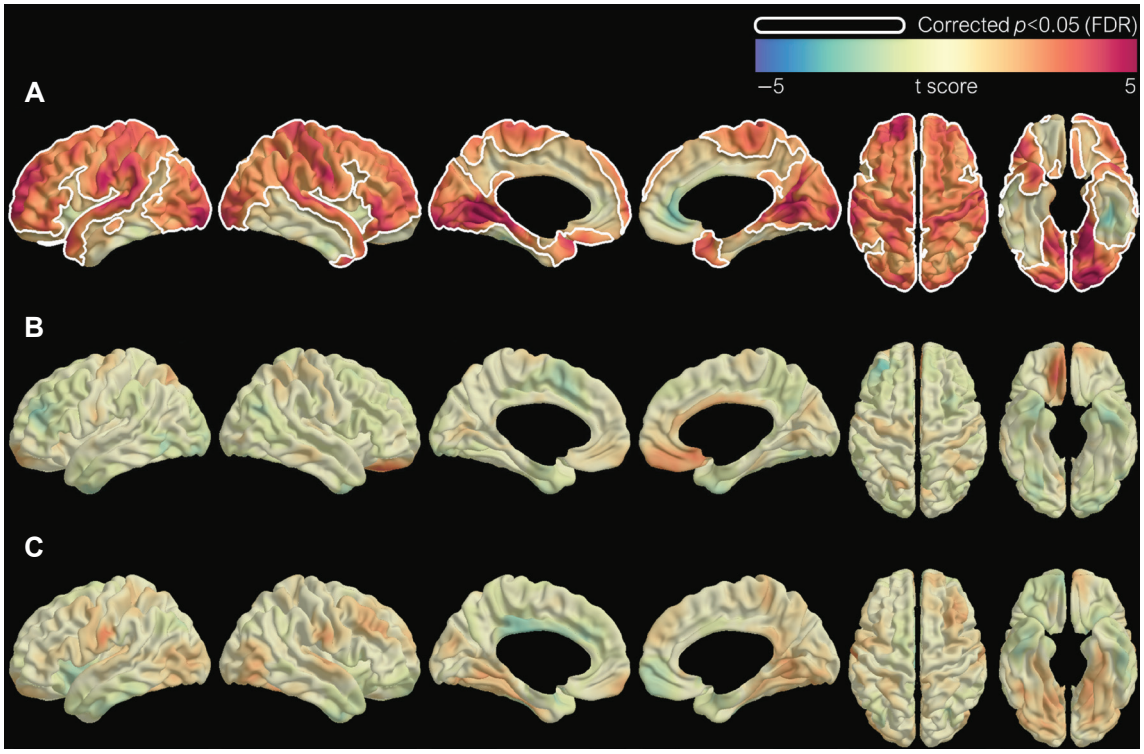

Fig. 1. Effects of demographic factors on regional cortical thickness. A vertexwise general linear model was used to find the effects of age (negative correlation) (A), education (positive correlation) (B), and sex (female-male) (C) on regional cortical thickness. The three predictors were simultaneously included in the statistical model. The brain regions delineated with white lines are significant after the corrections with the false discovery rate (FDR) method for multiple tests across multiple vertices.

ions, and Velcro straps to minimize motion artifacts. A high-resolution T1-weighted MRI volume data set was obtained from all subjects using a three-dimensional T1-TFE sequence configured with the following acquisition parameters: axial acquisition with a 224×256 matrix, 256×256 reconstructed matrices with 182 slices, 220 mm field of view, 0.98×0.98×1.2 mm^3 voxels, 4.6 milliseconds echo time, 9.6 milliseconds repetition time, 8° flip angle, and 0 mm slice gap. FDG-PET scans were performed using a Discovery 600 scanner (General Electric Healthcare, Milwaukee, MI, USA). FDG-PET scans were performed according to the following protocol: Approximately 4.1 MBq/kg (body weight) 18F-FDG was administered intravenously to the patient. After a 60-minute uptake period, PET images were acquired for 15 minutes. A spiral computed tomography scan was performed for attenuation correction with a 0.8 second rotation time at 60 mA and 120 kVp, and with 3.75 mm section thickness, 0.625 mm collimation, and 9.375 mm table feed per rotation. FDG-PET images were reconstructed using the ordered subset expectation maximization algorithm with 4 iterations and 32 subsets.

Amyloid positivity was assessed using a surface-based PET image analysis based on the cutoff value of the global standardized uptake value ratio of 1.478.[18] The detailed methods of FBB-PET image analysis were reported for our previous study.[2] DAT-PET and FDG-PET were assessed by a nuclear medicine physician (M.Y.) using visual interpretation. DAT-PET image interpretation was based on a dichotomous classification (normal/abnormal), with homogeneous and symmetrical striatal DAT uptake regarded as normal and asymmetrically or subregionally decreased striatal DAT uptake regarded as abnormal.[19] FDG-PET image interpretation was also dichotomous, and based on visual assessments of spatial patterns in FDG uptake and the degree of alterations.[20]

Cortical thickness measurement

We used the CIVET pipeline (http://mcin.ca/civet/) to measure the cortical thickness. In brief, the T1-weighted image of each subject was corrected for intensity inhomogeneities and linearly registered to the Alzheimer's Disease Neuroimaging Initiative (ADNI) atlas of the Montreal Neurological Institute (MNI), which is a T1-weighted template for older adults.[21,22] The images were then classified based on tissue type,[23] and the inner and outer cortical surfaces were extracted, resulting in 40,962 vertex points per hemisphere.[24] Cortical thickness was calculated as the Laplacian distance between the linked vertices of the inner and outer surfaces. The measured cortical thickness was smoothed using a surface-based diffusion smoothing kernel (full width at half maximum [FWHM] of

30 mm). The mean lobar cortical thickness was calculated for the frontal, temporal, parietal, and occipital cortices. One participant was further excluded due to insufficient data quality for the cortical thickness analysis, and 70 participants were finally analyzed in the study.

FDG-PET processing

We linearly registered FDG-PET images to individual T1-weighted MRI using rigid-body transformation. We then spatially normalized the images to the ADNI-MNI atlas using nonlinear warping fields acquired in the T1-weighted image processing stage, and then smoothed them using a FWHM of 4 mm with a Gaussian kernel. To calculate the FDG subject residual profile (FDG-SRP), each data set was transformed into its logarithmic form, and the data matrix was centered by subtracting the mean of each subject and the group mean voxel profile from the data.[25] The gray matter (GM) probability map obtained from the tissue classification was nonlinearly transformed into the ADNI-MNI atlas. We averaged all individual GM probability maps and assigned each voxel to either the foreground or background by binarizing more than 30% of the map to generate a study-specific GM mask. Statistical analyses of the FDG-SRP were performed within this GM mask. The mean lobar FDG-SRP was calculated for the frontal, temporal, parietal, and occipital cortices based on the automated anatomical labelling atlas.[26]

Statistical analyses

Statistical analyses for demographic and clinical data were performed using the Statistical Package for the Social Sciences (version 26.0, IBM, Chicago, IL, USA). We used the SurfStat toolbox (http://www.math.mcgill.ca/keith/surfstat/) developed at the MNI to perform vertex- and voxelwise statistical analyses. General linear models (GLMs) for vertexwise cortical thickness and voxelwise FDG-SRP were performed to evaluate the independent effects of age, sex, and education. The regional cortical thickness was analyzed by adding the intracranial volume (ICV) to the statistical model to account for individual differences in head size. The false discovery rate (FDR) method was used to correct for multiple statistical tests across multiple vertices or voxels.

The effects of demographic factors on the mean lobar cortical thickness and brain glucose metabolism were evaluated using GLMs with age, sex, and education as predictors. The effects of mean lobar cortical thickness and brain glucose metabolism on neuropsychological test scores were then evaluated using GLMs after controlling for age, sex, and education. All GLMs for the mean cortical thickness itself and for the mean cortical thickness as a predictor further included the ICV in the statistical models. The FDR method was used to correct for multiple comparisons across 4 lobes or 13 neuropsychological test scores.

RESULTS

Demographics and imaging characteristics of study participants

The 70 participants included 35 males. The age was 63.71±8.67 years (mean±standard deviation), and they had received 15.24±3.77 years of education. The total K-MMSE score was 29.27±0.93. Detailed demographic and imaging characteristics of study participants are presented in Table 1 and Supplementary Fig. 2 (in the online-only Data Supplement).

Effects of demographic factors on regional cortical thickness and brain metabolism

Evaluating the effects of age, education, and sex on regional cortical thickness and brain metabolism revealed that age was negatively correlated with cortical thickness in many regions except for the lateral temporal and medial frontal lobes (Fig. 1). Sex and education had no significant effects on regional cortical thickness. Age was negatively correlated with regional brain metabolism in the frontal, temporal, and parietal lobes, but positively correlated with regional metabolism in the pons, cerebellum, basal ganglia, thalamus, and several cortical areas mostly in the frontal, parietal, and occipital regions (Fig. 2). Sex and education were not associated with any regional brain metabolism.

Table 1. Demographic and imaging characteristics

Characteristic	Value
Number	70
Age (yr)	63.71±8.67
Sex, male:female	35:35
Education (yr)	15.24±3.77
K-MMSE score	29.27±0.93
Frontal thickness (mm)	2.93±0.10
Temporal thickness (mm)	3.06±0.09
Parietal thickness (mm)	2.76±0.13
Occipital thickness (mm)	2.61±0.18
Frontal metabolism	-0.08±0.02
Temporal metabolism	-0.08±0.02
Parietal metabolism	-0.08±0.03
Occipital metabolism	-0.08±0.04
ICV (mL)	1,368±142

Data are *n* or mean±standard deviation values.
ICV, intracranial volume; K-MMSE, Korean version of the Mini-Mental State Examination.

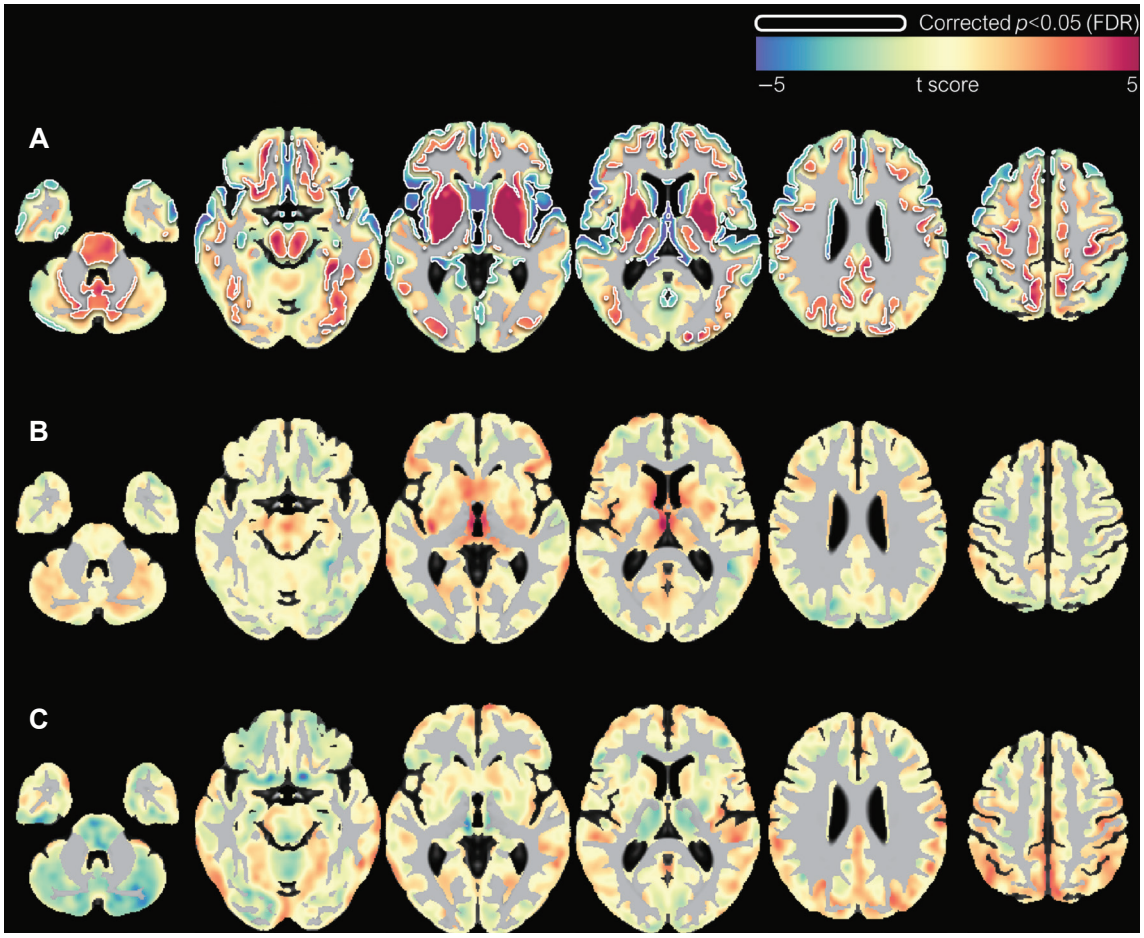

Fig. 2. Effects of demographic factors on regional brain glucose metabolism. A general linear model was used to determine the effects of age (positive correlation) (A), education (negative correlation) (B), and sex (female-male) (C) on regional brain glucose metabolism. The three predictors were simultaneously included in the statistical model. The brain regions delineated with white lines are significant regions after the corrections with the false discovery rate (FDR) method for multiple tests across multiple voxels.

Predictors of mean lobar cortical thickness and brain glucose metabolism

Evaluating the effects of age, education, and sex on mean lobar cortical thickness revealed that age was negatively correlated with the mean lobar cortical thickness in the frontal, temporal, parietal, and occipital cortices (Table 2). Sex and education were not associated with the mean cortical thickness. ICV was positively correlated with the mean cortical thickness in the frontal, temporal, and occipital lobes.

GLM analysis for mean lobar brain glucose metabolism indicated that age was negatively correlated with the mean temporal lobe metabolism (Table 2). The mean level of parietal lobe metabolism was higher in female than in male subjects. Education had no significant effect on the mean lobar brain metabolism.

Effects of mean lobar cortical thickness and brain metabolism on neuropsychological test scores

The mean lobar cortical thickness was not significantly associated with neuropsychological test scores in any of the four lobar regions (Table 3). However, the mean temporal metabolism was positively correlated with the immediate and delayed recall items of SVLT (Table 4).

DISCUSSION

This study evaluated the effects of demographic factors on cortical thickness and brain glucose metabolism and their relationships with cognition in healthy aging subjects. The major findings of our study were as follows: First, age was negatively correlated with cortical thickness in many cortical regions and with decreased mean brain glucose metabolism in the temporal lobe. Second, female subjects had higher cortical metabolism in the parietal lobe than did male subjects, while their mean cortical thicknesses were comparable. Third, the mean temporal metabolism was positively correlated with memory function, while the mean lobar cortical thickness was not associated with cognition scores. Together our results

Table 2. Predictors of mean lobar cortical thickness and brain glucose metabolism

Predictor	Frontal			Temporal			Parietal			Occipital		
	B (SE)	b	*p*	B (SE)	b	*p*	B (SE)	b	*p*	B (SE)	b	*p*
Age	-0.004 (0.001)	-0.369	0.001*	-0.004 (0.001)	-0.412	<0.001*	-0.006 (0.002)	-0.398	0.001*	-0.010 (0.002)	-0.462	<0.001*
Male	2.14×10^{-4} (0.024)	0.001	0.993	-0.017 (0.023)	-0.092	0.471	-0.008 (0.035)	-0.032	0.811	-0.043 (0.044)	-0.120	0.327
Education	-2.71×10^{-4} (0.003)	-0.011	0.926	-0.002 (0.003)	-0.092	0.429	-9.38×10^{-5} (0.004)	-0.003	0.982	-0.003 (0.005)	-0.058	0.601
ICV	2.39×10^{-4} (9.61×10^{-5})	0.357	0.016*	2.52×10^{-4} (9.32×10^{-5})	0.390	0.009*	2.22×10^{-4} (1.41×10^{-4})	0.239	0.121	4.92×10^{-4} (1.77×10^{-4})	0.385	0.007*
Predictor	Frontal metabolism			Temporal metabolism			Parietal metabolism			Occipital metabolism		
	B (SE)	b	*p*	B (SE)	b	*p*	B (SE)	b	*p*	B (SE)	b	*p*
Age	-0.001 (3.22×10^{-4})	-0.213	0.089	-0.001 (3.34×10^{-4})	-0.344	0.005*	3.09×10^{-4} (3.85×10^{-4})	0.092	0.426	0.001 (0.001)	0.168	0.186
Male	0.006 (0.005)	0.140	0.254	-0.006 (0.006)	-0.119	0.316	-0.026 (0.007)	-0.445	<0.001*	-0.002 (0.009)	-0.033	0.791
Education	7.04×10^{-5} (0.001)	0.012	0.925	0.001 (0.001)	0.088	0.468	0.001 (0.001)	0.149	0.202	0.001 (0.001)	0.128	0.318

Data are results of GLMs for mean lobar cortical thickness and mean brain glucose metabolism. Age, sex (male vs. female), and education were used as predictors. ICV was further included as a predictor for cortical thickness analyses.
*p values were significant at <0.05 after correcting for multiple comparisons across the four lobes using the FDR method.
B, unstandardized coefficient; b, standardized coefficient; FDR, false discovery rate; GLM, general linear model; ICV, intracranial volume; SE, standard error.

suggest that demographic factors affect cortical thickness and brain glucose metabolism differently and should therefore be considered when analyzing brain atrophy and glucose metabolism.

Higher age was associated with cortical thinning in many cortical regions. Aging is a powerful predictor of brain atrophy.[27,28] However, the effect of aging has varied among studies.[8-11] These differences suggest that the aging effect on cortical thinning is not consistent in the brain. The pathology study indicated that both frontal and temporal cortical thickness decreased with aging; however, the frontal lobe had steeper age-related decreases in cortical thickness than did the temporal lobe. In this study, higher age was associated with cortical thinning in many cortical regions; however, the effect size was not consistent among cortices. Considering the standardized coefficient β, the age effect was prominent in the frontal, temporal, and occipital cortices, suggesting that these regions were the core of the aging process.

In our study, aging was associated with decreased mean temporal glucose metabolism. Although voxelwise analysis indicated a negative correlation between age and brain metabolism in many cortical regions (Fig. 2), there was also a positive correlation mostly in the frontal, parietal, and occipital regions. Our study was consistent with previous studies in finding that the temporal lobe was vulnerable to age-related change.[9] It was particularly interesting that aging was related to increased brain metabolism in the pons, cerebellum, basal ganglia, thalamus, and some cortical regions. Age-related hypermetabolic patterns have also been reported in previous studies.[29-31] Considering that regional hypermetabolism related to aging is prominent in the cerebellum, basal ganglia, and motor cortex, aging-related regional hypermetabolism could be associated with reduced motor control inhibition.[32] Hypermetabolism was also found to be related to tau deposition in patients with MCI and low amyloid levels,[33] and with other degenerative diseases including frontotemporal dementia[34] and DLB.[35] Although we excluded subjects with significant amyloid deposition, we cannot completely exclude the possibility of preclinical neurodegenerative processes.

Female sex was associated with higher cerebral glucose metabolism in the parietal cortex, which is consistent with previous studies finding higher global[36] and parietal[9] brain metabolism in females than in males. This sex-related metabolic difference might be explained by biological factors (i.e., sex chromosomes or hormones) or social factors (i.e., smoking or alcohol consumption). However, since we did not compare the brain metabolic differences among younger patients (premenopause, <45 years old) or the exact statuses of social factors, further studies are needed. There was also no sex-related difference in cortical thickness. Only one previous study that

Table 3. Effects of mean lobar cortical thickness on neuropsychological test scores

	Frontal		Temporal		Parietal		Occipital	
	B (SE)	*p*	B (SE)	*p*	B (SE)	*p*	B (SE)	*p*
Digit-span backward	-0.01 (2.05)	0.996	0.58 (2.11)	0.787	-0.07 (1.39)	0.962	-1.09 (1.11)	0.329
K-BNT	-1.41 (5.54)	0.800	-0.27 (5.71)	0.963	0.56 (3.77)	0.882	0.81 (3.01)	0.789
RCFT copy	-0.82 (2.05)	0.693	0.59 (2.12)	0.781	-0.42 (1.40)	0.764	-1.06 (1.11)	0.342
SVLT immediate recall	-1.09 (5.86)	0.853	-8.32 (5.96)	0.167	1.31 (3.98)	0.744	3.06 (3.17)	0.338
SVLT delayed recall	-1.82 (2.75)	0.512	-3.29 (2.82)	0.247	-0.91 (1.87)	0.630	0.51 (1.50)	0.738
SVLT recognition	0.58 (2.10)	0.782	-1.47 (2.16)	0.499	1.75 (1.41)	0.218	1.64 (1.12)	0.150
RCFT immediate recall	0.32 (6.27)	0.959	-0.38 (6.47)	0.953	0.24 (4.26)	0.955	0.64 (3.41)	0.851
RCFT delayed recall	0.74 (6.10)	0.904	3.24 (6.28)	0.608	1.09 (4.15)	0.793	0.41 (3.32)	0.903
RCFT recognition	2.07 (2.22)	0.355	3.50 (2.27)	0.128	2.08 (1.50)	0.171	1.64 (1.20)	0.177
COWAT animal	-9.65 (6.74)	0.157	-5.15 (7.03)	0.467	-6.20 (4.59)	0.181	-3.15 (3.70)	0.398
COWAT supermarket	-9.54 (7.38)	0.201	-6.37 (7.67)	0.409	-8.35 (4.97)	0.098	-8.97 (3.91)	0.025
COWAT phonemic	8.72 (11.17)	0.438	0.60 (11.57)	0.959	-5.17 (7.60)	0.499	-3.22 (6.09)	0.600
Stroop color reading	2.48 (21.61)	0.909	4.53 (22.29)	0.840	-12.59 (14.61)	0.392	1.63 (11.76)	0.891

Data are results of GLMs for neuropsychological test scores after controlling for age, sex, education, and ICV. There were no p values that were significant (<0.05) after correcting for multiple comparisons across 13 neuropsychological tests using the FDR method.
COWAT, Controlled Oral Word Association Test; FDR, false discovery rate; GLM, general linear model; ICV, intracranial volume; K-BNT, Korean version of the Boston Naming Test; RCFT, Rey–Osterrieth Complex Figure Test; SE, standard error; SVLT, Seoul Verbal Learning Test.

Table 4. Effects of mean lobar glucose metabolism on neuropsychological test scores

	Frontal		Temporal		Parietal		Occipital	
	B (SE)	*p*	B (SE)	*p*	B (SE)	*p*	B (SE)	*p*
Digit-span backward	-6.02 (7.17)	0.404	-6.03 (6.92)	0.387	-10.93 (5.87)	0.067	-9.26 (4.35)	0.037
K-BNT	-0.83 (19.54)	0.966	13.50 (18.79)	0.475	14.44 (16.23)	0.377	26.93 (11.72)	0.025
RCFT copy	-1.63 (7.18)	0.821	-14.95 (6.68)	0.029	-1.79 (6.00)	0.766	7.33 (4.39)	0.100
SVLT immediate recall	8.12 (20.61)	0.695	52.23 (18.84)	0.007*	10.72 (17.19)	0.535	-14.86 (12.74)	0.248
SVLT delayed recall	8.60 (9.65)	0.376	29.16 (8.64)	0.001*	-0.24 (8.11)	0.976	-6.78 (6.00)	0.263
SVLT recognition	4.25 (7.44)	0.570	16.27 (6.91)	0.022	10.12 (6.10)	0.102	-0.86 (4.65)	0.854
RCFT immediate recall	-9.81 (22.00)	0.657	-6.95 (21.25)	0.745	0.24 (18.41)	0.990	-14.88 (13.62)	0.279
RCFT delayed recall	-24.73 (21.12)	0.246	-2.42 (20.60)	0.907	22.43 (17.61)	0.207	-6.64 (13.29)	0.619
RCFT recognition	-7.21 (7.77)	0.357	4.00 (7.53)	0.597	6.29 (6.49)	0.335	2.68 (4.87)	0.584
COWAT animal	-15.14 (23.86)	0.528	16.75 (23.01)	0.469	-10.89 (19.95)	0.587	7.90 (14.90)	0.598
COWAT supermarket	-27.71 (26.02)	0.291	17.82 (25.24)	0.483	-24.94 (21.71)	0.255	-3.04 (16.37)	0.853
COWAT phonemic	0.20 (39.32)	0.996	-4.53 (37.95)	0.905	-53.09 (32.19)	0.104	-29.50 (24.26)	0.228
Stroop color reading	45.17 (76.36)	0.556	81.16 (73.22)	0.272	77.29 (63.25)	0.226	63.21 (47.13)	0.185

Data are results of GLMs for neuropsychological test scores after controlling for age, sex, and education.
*p values were significant at <0.05 after correcting for multiple comparisons across 13 neuropsychological tests by using the FDR method.
COWAT, Controlled Oral Word Association Test; FDR, false discovery rate; GLM, general linear model; K-BNT, Korean version of the Boston Naming Test; RCFT, Rey–Osterrieth Complex Figure Test; SE, standard error; SVLT, Seoul Verbal Learning Test.

we are aware of simultaneously evaluated brain atrophy and metabolic changes related to demographic factors in normal aging,[9] which also indicated that sex-related changes in brain atrophy and metabolism are not completely parallel. Our results suggest that changes in brain metabolism are more sensitive to sex-related factors than structural changes.

This study had several limitations. First, the age distribution was not even, since 51 of 70 subjects (72.9%) were younger than 69 years (but older than 50 years old), 14 (20.4%) were between 70 and 79 years old, and only 5 (7.1%) were older than 80 years. The inclusion of more subjects with normal cognition is needed to establish mean cortical thickness values for those aged 70–89 years. Second, the mean education duration was too long to represent the general population, which limits the generalizability of our results. Third, not all subjects underwent FBB-PET and FP-CIT-PET simultaneously. Although all subjects showed normal visual results in FDG-PET, we cannot exclude the possibility that very early changes in degenerative diseases had already begun. There were also several neurodegenerative disorders that were not

associated with amyloid pathology, dopaminergic depletion, or abnormal brain glucose metabolism; we therefore cannot exclude the possibility of these diseases having effects. Notwithstanding these limitations, our results suggest that demographic factors affect cortical thickness and brain glucose metabolism differently in normal aging, and therefore the effects of demographic factors must be considered when interpreting the results obtained in studies of the cortical thickness and brain metabolism.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2022.0021.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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