

Gray and White Matter Volume Reductions Associated with Aging in Healthy Korean Adults after Exclusion of White Matter Hyperintensity: A Voxel-Based Morphometric Study

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Background: Understanding the changes of brain volume due to normal aging in healthy adults may help us better appreciate the age-related changes in the brain associated with neurodegenerative diseases. The objectives of our current study are: 1) to evaluate the volumes of gray matter, white matter and cerebrospinal fluid in healthy adult with exclusion of white matter hyperintensity and 2) to identify their regional changes in which there have been controversies. **Methods:** We performed a cross-sectional analysis of magnetic resonance images from 108 normal Korean subjects (42-80 yr of age) using voxel-based morphometry. **Results:** Global volumes of each tissue revealed no change between 5th and 6th decade and their declines afterward. There were negative correlations between gray matter (3.04 cm³/yr) and white matter volume (2.31 cm³/yr) and increasing age, and a positive correlation between CSF volume (5.56 cm³/yr) and increasing age. Gray matter, white matter and CSF volume normalized with total intracranial volume demonstrated changes at 0.21%/yr, 0.16%/yr and 0.36%/yr respectively. Gray matter volume was reduced in the frontal, parietal and temporal lobes with increasing age, but not in the medial temporal lobes or posterior cingulate. White matter losses occurred in the anterior corpus callosum, frontal and other periventricular areas. **Conclusions:** These findings provide essential information on the rates and regional patterns of age-related changes in brain volume for a healthy Asian population, which can serve as a baseline for comparison with other pathologic conditions.

Key Words: Aging, Voxel-based morphometry, Gray matter volume, White matter volume

INTRODUCTION

Normal aging is associated with brain atrophy. Identifying such a change can provide insight into the cognitive changes associated with aging and Alzheimer disease (AD) progression, and may enhance our assessment of the effectiveness of interventions that target areas of brain shrinkage related to

functional loss.

Several studies have reported global volume decreases in gray matter (GM) with age. Cross-sectional and longitudinal studies have identified regional GM volume reductions in the insula, cerebellum, basal ganglia, thalamus, and prefrontal, parietal and temporal association cortices [1, 2]. However, evidences of white matter (WM) volumetric changes were

inconsistent [2-6]. Furthermore, some studies have found that volumetric changes in the amygdala, hippocampus and cingulate gyrus are associated with normal aging, which are area specific in AD [7-10], but others have not [4, 5, 11-13].

The evidence regarding brain tissue loss in the aging process is mixed. It is unclear whether the observed differences in brain volume are truly consistent across studies. Inconsistencies may be due to differences in measurements of tissue loss used across studies (e.g., absolute vs. relative quantities, or *r*-values rather than loss rates) and subjects' characters (e.g., age range or WM hyperintensity). White matter hyperintensity (WMHI) is also commonly observed on magnetic resonance imaging (MRI) in the elderly. It has been shown that ischemia may lead to accelerated GM and WM changes [14]. A small age range restricted to the elderly might increase variability in brain volume, leading to decreased power in detecting significant changes in brain volume associated with aging. Brain volume in normal aging begins to decline around the age of 40 yr. Accordingly, we conducted the present study to better understand age-related changes in normal, healthy brains in adult Koreans between the age of 40 to 80 yr.

One would expect that GM volume changes in normal healthy aging differ from that in AD, but there had been controversies especially in the amygdala, hippocampus and cingulate gyrus. Therefore, we conducted the present study to determine whether the regional GM volume changes with specific attention in these areas. In addition, because there were also inconsistencies in the literatures on whether WM volume change and WMHI could affect on the brain volume change, we sought to determine the rate of WM volume reduction in healthy aging by excluding those with WMHI. We localized volume reductions in separate brain structures and evaluated global WM and GM volume changes occur in normal, healthy brains in adult Koreans between the age of 40 to 80 yr.

Identifying such changes will provide insights into aging and pathologic changes of neurodegenerative disorders, and will enhance assessments of effectiveness of interventions that target brain shrinkage to improve functional abilities.

MATERIALS AND METHODS

1. Subjects

We recruited healthy subjects who visited the health-promotion center of Chung-Ang University Hospital between March 2008 and February 2009. All subjects completed a standardized assessment protocol, including a detailed medical history, physical and neurological examinations and blood tests (e.g., hemoglobin, white cell count, serum electrolytes, glucose, urea, creatinine, liver function tests, thyroid stimulating hormone and free thyroid hormone, and vitamins B1, B6, and B12). All subjects also completed the Korean version of the Mini-Mental State Examination (K-MMSE) and participated in an MRI brain scan.

The inclusion criteria for healthy subjects were as follows: 1) age 40 yr or older, 2) no complaints of memory impairment by subjects or their first degree relatives, 3) no functional impairment affecting daily living, 4) a K-MMSE score of 27-30, and 5) no evidence of concurrent disease that would have caused any cognitive impairment. Exclusion criteria included: individuals with histories of substance abuse, major head injuries, major psychiatric illnesses, medical illnesses (e.g. non-stable diabetes mellitus or uncontrolled severe hypertension), chronic infectious disease, stroke or transient ischemic attack, encephalitis, meningitis and epilepsy.

A total of 137 subjects completed the MRI brain scan. All MRI images were evaluated by qualified radiologists. On the FLAIR images, we semi-quantitatively rated the severity of WMHI, according to the modified Fazekas's or Shelten's criteria proposed by the Clinical Research for Dementia of South Korea [15, 16]. Periventricular hyperintensities (PVH) and the deep white matter hyperintensities (DWH) were evaluated separately. We recruited healthy control subjects into the final sample whose MRIs demonstrated less than 10 mm DWH and maximum diameters adjacent to the anterior and posterior horns (capping) or the lateral ventricles (bands) of less than 10 mm.

Twenty nine people excluded because of excessive WMHI, and our final sample consisted of 108 healthy subjects (mean age = 59.4 ± 9.3 yr). None showed memory or cognitive impairment at the time of the scan. Mean K-MMSE score was

28.6 ± 1.3 and mean education duration was 9.6 ± 6.8 yr for our sample. All study subjects gave written informed consent to allow their clinical data to be used for research purposes. This study was approved by the Institutional Review Board (IRB) of hospital.

2. Data acquisition and analysis

Scanning was performed on a Philips Intera Achieva 3.0 T scanner (Philips: Amsterdam, Netherlands). Images were acquired using T1-weighted, T2-weighted, fluid-attenuated inversion recovery (FLAIR) and T1-weighted 3D volumetric spoiled gradient echo sequences (TI: 800 ms; TR: 2000 ms; TE: 20 ms; slice resolution: $0.5 \text{ mm} \times 0.5 \text{ mm}$; slice thickness: 0.5 mm).

We performed volumetric analyses using the VBM5 Toolbox (<http://dbm.neuro.uni-jena.de/vbm/vbm5-for-spm5/>) and Statistical Parametric Mapping 5 (SPM 5, <http://www.fil.ion.ucl.ac.uk/spm/>) software packages. For quantitative analyses of the whole brain, images were analyzed using the VBM5 Toolbox protocol: normalization, bias-correction, segmentation, and smoothing. Differences between MRI images of each subject were corrected through normalization. Images were normalized to the ICBM template for East Asian brains. For modulated normalization, we chose 'Non-linear only' option of the VBM5 toolbox, which produces tissue class images in alignment with the template, but multiplies the voxel values by the non-linear components only. This is useful for VBM analyses because it allows comparison of the absolute amount of tissue corrected for individual brain sizes (<http://dbm.neuro.uni-jena.de/vbm/vbm5-for-spm5/manual/>, <http://dbm.neuro.uni-jena.de/vbm8/VBM8-Manual.pdf>). Images were then segmented into GM, WM and CSF using tissue probability maps '*gray.nii*', '*white.nii*', and '*csf.nii*' in the SPM 5 templates. Image homogeneity was assessed and the total intracranial volume (TIV) of each subject was obtained from his or her modulated GM, WM and CSF. All images were smoothed using a 12 mm FWHM isotropic Gaussian kernel to minimize cortical variation of the gyrus, which depends on individual characteristics.

3. Statistical global analysis

For analyses of global volume changes, we calculated the global volumes of GM, WM and CSF using 'Calculate raw volumes for GM/WM/CSF' of the VBM5 toolbox, and normalized each tissue volume with TIV for each subject, which was calculated as the sum of the GM, WM, and CSF. The normalization of tissue volumes was conducted by dividing the GM, WM and CSF volume by the TIV. This procedure controls for variation in brain sizes across subjects.

Statistical analyses were performed using the R software package (R Foundation for Statistical Computing; version 2.11). For all analyses, the significance threshold was set at $p < 0.05$. Bivariate correlation analyses were performed to assess the relationship between normalized volume change of each tissue type and age.

4. Statistical parametric maps

Statistical parametric maps of GM and WM volume change with age were analyzed using an ANCOVA model with age as the covariate. Global normalization was performed with TIV as a nuisance effect. The absolute threshold masking was 0.1. To correct for multiple comparisons, we used a family-wise error (FWE) of 0.01 with a voxel extent threshold of 500. Tissue maps reflected the probabilities of voxels being GM or

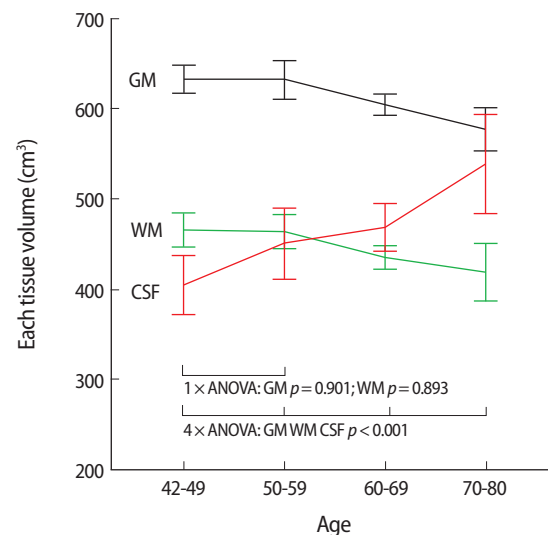


Fig. 1. Each tissue of brain volume differences between 5th, 6th, 7th and 8th decade. GM, gray matter; WM, white matter; CSF, cerebrospinal fluid.

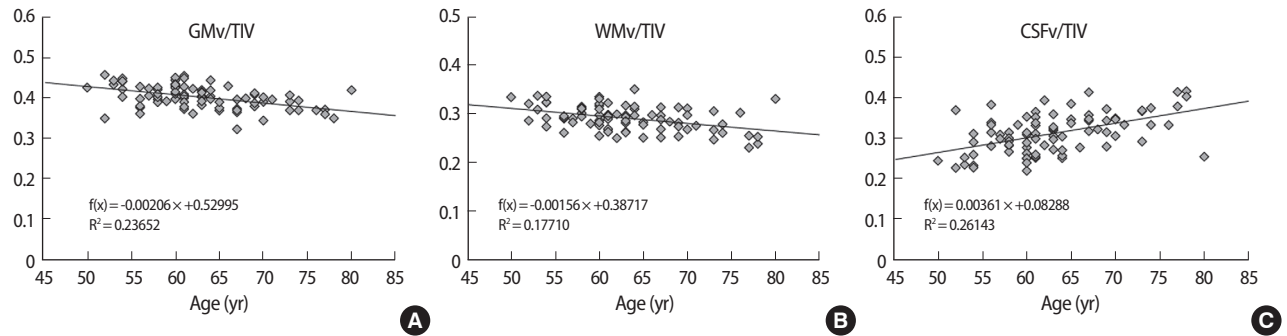


Fig. 2. Correlations between age and (A) gray matter, (B) white matter, and (C) CSF volume after normalization ($p < 0.001$). GMv/TIV, normalized gray matter volume with total intracranial volume; WMv/TIV, normalized white matter volume with total intracranial volume; CSFv/TIV, normalized cerebrospinal fluid volume with total intracranial volume; TIV, total intracranial volume.

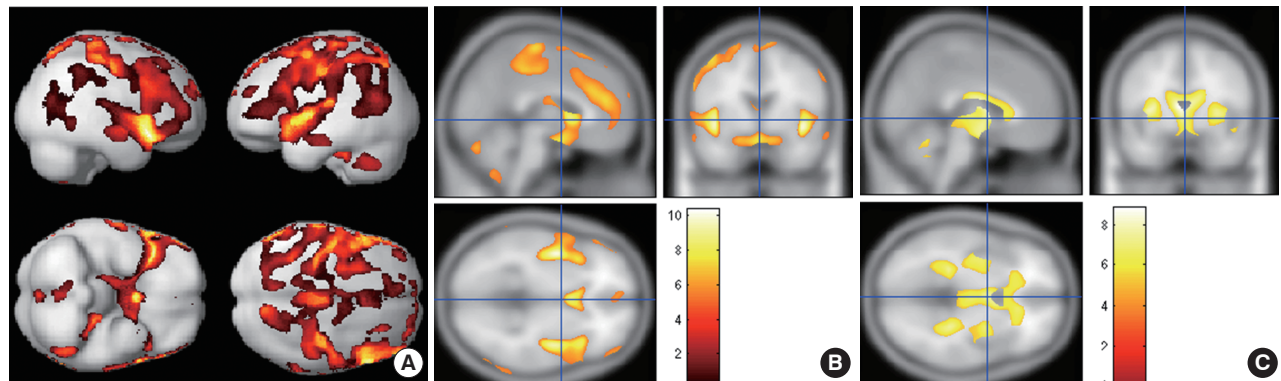


Fig. 3. T-probability map of regional volume change of (A) rendering and (B) sectional images of gray matter and (C) sectional images of white matter with age (family-wise error corrected $p < 0.01$).

WM. The values reflected the probabilities of individual voxels and were scaled in proportion to volume change. Near-anatomic brain MR image registration based on Talairach reference system was used [17].

RESULTS

1. Global changes in volume of GM, WM and CSF

Mean GM volumes in age of 42-49 group ($n = 22$), 50-59 group ($n = 24$), 60-69 group ($n = 47$) and 70-80 group ($n = 15$) were $633.1 \pm 35.7 \text{ cm}^3$, $631.5 \pm 52.6 \text{ cm}^3$, $604.5 \pm 40.1 \text{ cm}^3$ and $577.25 \pm 42.7 \text{ cm}^3$, and mean WM volume were $465.1 \pm 41.6 \text{ cm}^3$, $463.3 \pm 41.7 \text{ cm}^3$, $433.9 \pm 41.8 \text{ cm}^3$ and $418.3 \pm 57.7 \text{ cm}^3$. GM and WM volumes were decreasing after age of 50-59, but there were no differences between age of 42-49 and

50-59 (Fig. 1). Therefore, we calculated the rate of absolute and normalized volume changes linearly from the age of 50 and over (Fig. 2). There was a significant negative correlation between GM/TIV and age; the calculated difference was 0.21% per year ($r^2 = 0.24$, $p < 0.001$) and a corresponding absolute decrease of 3.04 cm^3 per year ($r^2 = 0.19$, $p < 0.001$). Normalized WM also showed a significant decrease of 0.16% per year ($r^2 = 0.18$, $p < 0.001$) and its absolute WM decrease rate was 2.31 cm^3 per year ($r^2 = 0.11$, $p < 0.001$). In addition, there was a significant increase in both CSF volume and CSF/TIV with age. Normalized CSF increased 0.36% per year ($r^2 = 0.26$, $p < 0.001$) and its absolute CSF increase rate was 5.56 cm^3 per year ($r^2 = 0.15$, $p < 0.001$; after age of 50). The normalized GM decrease rate, when added to the normalized WM rate, exactly matched the rate of CSF increase. There was no relationship between TIV and age ($r^2 = 0.00$; $p = 0.513$).

Table 1. Area of gray matter density reduction in healthy aging after controlling for the global effect of total intracranial volume (family-wise error corrected $p < 0.01$)

Coordinates x, y, z			Anatomical location	Z-score
36	16	-15	Right inferior frontal gyrus	Infinite
-43	-5	1	Left insula	Infinite
43	-1	-5	Right insula	Infinite
-5	15	4	Left caudate	7.83
-55	21	30	Left middle frontal gyrus	7.71
7	17	5	Right caudate	7.15
12	-71	59	Right superior parietal lobule	6.89
39	-18	48	Right precentral gyrus	6.70
-63	-25	44	Left postcentral gyrus	6.56
2	-24	69	Right medial frontal gyrus	6.53
5	-32	51	Right frontal paracentral lobule	6.52
5	-21	49	Right medial frontal gyrus	6.49
-1	42	19	Left medial frontal gyrus	6.48
-62	-64	20	Left superior temporal gyrus	6.40
-44	-2	57	Left precentral gyrus	6.40
-18	-31	-20	Left cerebellum anterior lobe	6.38
48	-30	53	Right postcentral gyrus	6.26
-57	-26	36	Left inferior parietal lobule	6.13
-35	-62	53	Left superior parietal lobule	5.92
-38	-49	54	Left inferior parietal lobule	5.92
-62	-65	11	Left middle temporal gyrus	5.82
3	15	43	Right medial frontal gyrus	5.63
26	-62	66	Right superior parietal lobule	5.60
-50	14	21	Left inferior frontal gyrus	5.57

2. Voxel-based morphometry of GM and WM

VBM results of GM and WM were mapped separately to assess changes in relation to age. Results for regional differences, after controlling for global differences, were reported for each tissue type. Both GM and WM volume decrease as age increases (Fig. 3).

1) Changes in GM volume

VBM analysis revealed a widespread effect of age on all lobes of the brain. The strongest effects were observed in the regions of the peri-Sylvian, insula, and dorso-lateral and medial frontal gyrus ($p < 0.01$, FWE corrected). Fig. 3A and B show areas of negative correlation between age and regional GM volume changes. We found bilateral atrophy in the following regions: insula (left and right: z score = positive infinite), inferior frontal gyri (right: z = positive infinite; left: z = 5.57), caudate nucleus (right: z = 7.15; left: z = 7.83), superior parietal lobule (right: z = 6.89; left: z = 5.92), precentral gyrus (right: z = 6.70; left: z = 6.40), medial frontal (right: z = 6.53;

left: z = 6.48), and postcentral gyrus (right: z = 6.26; left: z = 6.56) (Table 1). Areas exhibiting little or no age effects (relative preservation) were noted in the amygdala, hippocampi, and entorhinal cortex.

2) Changes in WM volume

Regional volume changes were observed in WM after controlling for TIV (Fig. 2C). Decrease in WM volume appears to be confined to the genu of the corpus callosum, and immediately adjacent to insula and ventricles.

DISCUSSION

Recent increased awareness of aging has raised interest in preserving brain function. Many studies have documented shrinkage of the human brain associated with aging. Examining volumetric changes in the brain can provide researchers with vital information that may eventually lead to treatments that decrease or reverse atrophy. Our study provides empirical information could aid in evaluating effectiveness of such interventions.

We found that GM and WM volume in our healthy Korean population did not change significantly up to the age range of 50-59, and then declined linearly afterwards. We calculated the rate of the volume changes from age 50 and over, and found an absolute GM volume decrease rate of 3.04 cm^3 per year and a normalized GM volume decrease rate of 0.21% per year.

We also determined the absolute and normalized WM decrease rate to be $2.31 \text{ cm}^3/\text{yr}$ and 0.16%/yr, a finding that does not converge with some prior studies. There are some discrepancies between studies regarding WM changes with age [4, 5, 18-21]. Several considerations should be noted. First, prior studies include subjects of varying age ranges. However, a larger age range including the youth would not show any significant decline prior to age 50, while a smaller age range restricted to the elderly might increase variability in WM volume, leading to decreased power in testing for a difference in WM volume change associated with aging. By contrast, our sample was drawn from an optimal age range (42-80 yr), which increased our power to detect differences. Second, previous

studies differ in the probability of including significant pathologies such as small-vessel ischemic disease, even without apparent cognitive dysfunction. In this study, we excluded scans demonstrating more than minimal WM ischemic changes on FLAIR images and from subjects who had abnormal MMSE score in order to minimize the chances of WM pathology affecting volumetric differences. It has been shown that ischemia may lead to accelerated GM and WM changes [14]. When we focused on age 50 and on (note: some previous studies included very young age such that when fitted into the linear model, their results were smaller than ours), we found that the rate of GM volume decline were similar to those reported in prior studies, which indicates that our sample is representative of healthy aging. Finally, differences in the statistical techniques used to perform VBM may be responsible for some of the discrepant findings.

Our regional analyses found modest GM decreases in the inferior, middle posterolateral and bi-frontal regions. We also found decreases in the bilateral insula, and temporal and parietal regions [22, 23]. However, we did not find GM losses in the medial temporal lobe or posterior cingulate, which are regions characteristically showing early losses in AD. We also found significant GM loss in the bilateral caudate. However, this loss may not reflect volumetric loss because age-related ventricular enlargement shifts the adjacent GM tissue (e.g. basal ganglia) outward and may cause misleading results with apparent reduction in volume in deep GM. In general, our findings converge with those of prior studies that also reported frontal regional GM and WM losses (referring to local GM and WM losses that exceed global losses) with age. These findings provide support for the theory of frontal selectivity in cognitive aging [20, 24].

The present study had a limitation that we did not analyze the gender difference in aging processes. Therefore, it would be necessary to recruit more subjects to explore the impact of sexual difference on brain volume change with age.

In conclusions, age related WM as well as GM volume reduction was significant after age of 50, with GM volume decreasing at a rate of 3.04 cm^3 per year (0.21% per year), WM volume decreasing at a rate of 2.31 cm^3 per year (0.16% per year), and CSF volume increasing at a rate of 5.56 cm^3 per year (0.36% per year) between age 50 to 80. Diffuse regional GM

volume reductions were observed with age, especially in the frontal, parietal and temporal lobes, but not in the medial temporal lobes or posterior cingulate. We also found focal WM losses in the anterior corpus callosum, frontal and other periventricular areas. These findings provide information on the rates and regional patterns of age-related changes in brain volume of East Asians and can serve as a baseline for comparison to other pathologic conditions in future studies.

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