Brain volume variations in postmenopausal women: A voxel-based morphometry (VBM) study

Tae-Hoon Kim[1] and Gwang-Woo Jeong[2]

[1]Research Institute of Medical Imaging, Chonnam National University Medical School, Gwangju, Korea, [2]Radiology, Chonnam National University Medical School, Gwangju, Korea

Synopsis: During the past two decades, several studies in females of animal models and human have been performed to unveil the reproductive system changes and the complex interactions with the ovaries. However, morphologic variations in the central nerve system following menopause have not yet been studied. Therefore, this study utilized voxel-based morphormetry (VBM) to evaluate the age-related changes and the effects of menopause on the brain volumes in postmenopausal women.

Subjects and Methods: A total of 48 right-handed subjects consisting of 24 nonpostmenopausal (mean age: 39.8±8.1) and 24 postmenopausal women (mean age: 55.5±2.5) took part in this study. All the subjects have no history of neurological and psychiatric illness. Menopause was defined as continuous amenorrhea for more than 12 months and follicle-stimulating hormone (FSH) level more than 30 mIU/mL.

The subjects underwent on MRI at a 3 Tesla (Siemens Tim Trio) with a transmit/receive birdcage head coil. Brain images were acquired using a 3-dimensional phase sensitive inversion recovery Turbo FLASH with the following parameters: TR/TI/TE=1700/900/2.2 ms; flip angle=9°; FOV=256×256 mm^2; matrix size=256×256; voxel size=1×1×1 mm^3. MR image data were processed by using SPM8 software with diffeomorphic anatomical registration through exponentiated Lie algebra(DARTEL) algorithm. Analyses were performed on gray matter(GM) segments; were multiplied by the non-linear components derived from the normalization matrix(modulated GM volumes); and then, smoothed with a Gaussian kernel of 6 mm full width at half maximum.

The total intracranial volume was measured by using 'spm_calc_ticv.m' function from segmented GM, WM and CSF images in each woman. The variation of brain volume between nonpostmenopausal and postmenopausal women was analyzed with independent two sample t-test and analysis of covariation (ANCOVA) with controlling ages. Significance threshold was set at $P=0.05$, corrected by family wise error (FWE) for multiple comparison.

Results and Discussion: Table 1 compared the total intracranial volumes(mL) of each tissue in nonpostmenopausal and postmenopausal women. The volumes in postmenopausal women averagely decreased GM 9.5 mL and WM 2.9 mL, whereas increased CSF 12.8 mL and total volume 0.4 mL.

Figure 1 shows the significant volume changes with the independent two sample t-test and ANCOVA for controlling aging (FWE, $P<0.05$) and the brain areas summarized in Table 2. Postmenopausal women show the prominent reduction in brain structures, however there was no increased brain volume.

Table 1. Comparison of the total intracranial volumes in nonpostmenopausal and postmenopausal women

Tissues / Groups	Total intracranial volumes (mL)*			
	GM (CV†, %)	WM (CV†)	CSF (CV†)	Total volume (CV†)
Nonpostmenopausal women (n= 24, A)	642.9±36.9 (5.6)	485.4±32.9 (6.6)	319.1±22.1 (6.6)	1447.4± 84.6 (5.7)
Postmenopausal women (n= 24, B)	633.4±44.1 (7.0)	482.5±41.1 (8.5)	331.9±32.1 (9.7)	1447.8±106.5 (7.4)
Group mean difference (A - B)	9.5	2.9	-12.8	-0.4
P-value‡	0.423	0.789	0.114	0.988

* The volume was measured by using 'spm_calc_ticv.m' function from segmented individual data on SPM8.
† The percentage indicates the coefficient of variation (CV = [SD / volume mean] × 100).
‡ The difference between nonpostmenopausal and postmenopausal women was analyzed with independent two sample t-test.
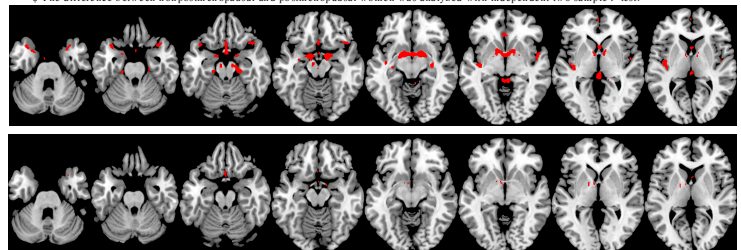
Table 2. Volume reduced areas in postmenopausal women

Anatomical area	Abbr.	t-value	MNI coordinate x	y	z	Laterality (%)	No. of Significant voxels Both side	Rt side	Lt side
A. Independent two sample t-test									
Hypothalamus	Hy	9.49	2	3	-6	7	193	90	103
Body of caudate nucleus	BCd	9.39	18	-22	21	-75	168	147	21
Amygdala	Amg	8.83	-17	1	-10	17	398	166	232
Superior temporal gyrus	STG	8.27	-36	15	-26	50	680	171	509
Globus pallidus	GP	8.15	-14	7	-5	31	319	110	209
Insula	Ins	7.96	-39	-18	0	91	784	36	748
Parahippocampal gyrus	PHG	7.84	21	-22	-20	1	414	204	210
Orbitofrontal gyrus	OFG	7.58	40	21	-18	-85	236	218	18
Lingual gyrus	LiG	7.31	5	-37	-3	-100	16	16	-
Vermis	Verm	7.24	5	-40	-6	-75	32	28	4
Gyrus rectus	GRe	7.21	0	20	-18	41	101	30	71
Hippocampus	Hi	6.85	19	-20	-17	-82	34	31	3
Superior frontal gyrus	SFG	6.68	-2	57	3	100	16	-	16
Heschl's gyrus	HeG	6.68	-39	-19	5	95	41	1	40
Anterior cingulate gyrus	ACgG	6.58	-2	33	-4	44	140	39	101
Rolandic operculum	RoO	6.56	-45	-10	8	-50	28	21	7
Pons	PONS	6.37	5	-9	-31	-100	16	16	-
Inferior frontal gyrus	IFG	6.26	46	19	-12	-85	26	24	2
B. ANCOVA for controlling aging									
Globus pallidus	GP	7.14	-17	1	4	100	83	-	83
Gyrus rectus	GRe	6.72	-2	22	-16	67	30	5	25
Hypothalamus	Hy	6.28	-5	3	-7	100	3	-	3
Fusiform gyrus	FuG	6.10	-30	-13	-31	100	2	-	2
Superior temporal gyrus	STG	6.07	30	13	-26	-86	14	13	1

Fig. 1. Comparison of the independent two sample t-test (A) and ANCOVA for controlling aging (B) (FWE corrected at $P<0.05$). Note that significant maps show the brain volume reductions in postmenopausal women.

Fig. 2 (Right). Comparison of the two sample t-test and ANCOVA for controlling aging. The dashed line indicates threshold t-value for significant maps (FWE at $P<0.05$, t-value= 5.96)

Figure 2 shows the comparison of two sample t-test and ANCOVA for controlling aging. In the postmenopausal women, the GM volume reductions are closely related with the deterioration of the brain functions including memory (hippocampus/ parahippocampal gyrus), emotional (amygdala/ body of caudate nucleus/ insula/ anterior cingulate gyrus), audio-visual (lingual gyrus/ Heschl's gyrus/ Rolandic operculum), and cognitive (orbitofrontal gyrus/ Inferior frontal gyrus) function. These regions are sensitive to brain aging because of the volume changes are correlated with aging and the statistical significance disappeared by ANCOVA for controlling the aging factor (Fig. 1B). Therefore, the atrophies in the regions of the globus pallidus, gyrus rectus, hypothalamus, fusiform gyrus and superior temporal gyrus are more important to the brain volume changes following menopause. It should be noticed the atrophy of the hypothalamus because the area controls the hypophysis and is involved in the secretion of sex hormones.

Conclusions: With the help of SPM8-VBM with DARTEL, this study finds out the regional gray matter atrophies in postmenopausal women. Therefore, these findings would be helpful for an understanding of an interaction of brain morphological changes related with aging and menopause.

References

1. Goto M et al. *Radiol Phys Technol* 2011; 4: 185-188.
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