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# Effects of Sex Hormones and Age on Brain Volume in Post-Menopausal Women

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ABSTRACT

**Background:** Investigation of the effect of sex hormones on the brain volume in women provides a unique opportunity to examine menopause-related morphometric alterations.

**Aim:** To evaluate brain morphological alterations in post-menopausal women using voxel-based morphometry and its correlations with sex hormone levels.

**Methods:** 20 Pre-menopausal women and 20 post-menopausal women underwent structural MRI.

**Outcomes:** T1-weighted magnetic resonance data were acquired and serum sex hormones including total estrogen, estriol, estradiol (E2), follicle-stimulating hormone, free testosterone, SHBG, and luteinizing hormone were measured.

**Results:** Post-menopausal women showed decreased gray matter (GM) in the supplementary motor area (SMA), inferior frontal gyrus, olfactory cortex, and superior temporal gyrus as contrasted with pre-menopausal women using analysis of covariance ($P < .05$). The GM volume (GMV) values of the SMA, inferior frontal gyrus, and superior temporal gyrus were positively correlated with the levels of E2 in the pre-menopausal and post-menopausal women, in which the volume of the SMA was negatively correlated with the duration of time after menopause in post-menopausal women.

**Clinical Translation:** This finding is potentially applicable to assess the brain dysfunction with morphological changes in post-menopausal women.

**Conclusions:** Our study is the first to evaluate a direct relationship between the level of E2 and GMV change. We directly compared pre-menopausal and menopausal women un-matched in age. This study highlights the menopause-related morphological alterations in post-menopausal women, suggesting that the reduced GMV were closely associated with the symptoms of menopause caused by the decreased levels of E2. **Kim G-W, Park K, Jeong G-W. Effects of Sex Hormones and Age on Brain Volume in Post-Menopausal Women. J Sex Med 2018;XX:XXX–XXX.**



**Key Words:** Age; Estradiol; Gray Matter; Menopause

## INTRODUCTION

Menopause is defined as the set of physiological events in women correlated with age and sex hormone levels during which menstruation ceases, resulting in the loss of follicular activity.[1,2] These physiological changes exert a wide variety of effects upon brain development and function.[3–5] For example, post-menopausal women have a higher risk of Alzheimer disease compared with men of the same age.[6] This sex difference may be correlated with the decrease in the levels of sex hormones in women after menopause.[7] Indeed, estrogen therapy (ET) in post-menopausal women ameliorates cognitive dysfunction and decreases the risk and/or severity of neurodegenerative conditions such as Alzheimer disease and stroke.[8]

Investigation of the effect of sex hormones on the brain volume in women provides a unique opportunity to examine menopause-related morphometric alterations. Especially, estrogen enhances the structural integrity of brain tissue, inducing neuronal growth and similar trophic effects. Accordingly, numerous morphometric studies[7,9,10] concerning post-menopausal women have focused on the effects of ET, demonstrated as enhanced cognitive function and brain volume. A voxel-based morphometry (VBM) study[9] demonstrated that post-menopausal women receiving ET had

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**Table 1.** Sex hormone levels in pre-menopausal and post-menopausal women

| Sex hormone | Pre-menopausal women (n = 20) | Post-menopausal women (n = 20) | *P* value |
|---|---|---|---|
| Total estrogen,* pg/mL | 549.2 ± 323.1 | 70.1 ± 33.9 | <.001** |
| Estradiol,† pg/mL | 208.4 ± 164.8 | 12.8 ± 5.8 | <.001** |
| Estriol,‡ pg/mL | 2.9 ± 1.7 | 2.3 ± 1.4 | .554 |
| Free testosterone,§ pg/mL | 0.4 ± 0.3 | 0.2 ± 0.2 | .971 |
| SHBG,‖ nmol/L | 102.3 ± 33.9 | 73.0 ± 20.9 | .051 |
| Follicle-stimulating hormone,¶ mIU/mL | 6.5 ± 4.2 | 66.1 ± 20.7 | <.001** |
| Luteinizing hormone,# mIU/mL | 14.7 ± 14.4 | 37.4 ± 12.6 | .006†† |

Data are presented as mean ± SD unless otherwise stated.
*P* values calculated by analysis of covariance with covariates of age.
Reference ranges for hormones in pre-menopausal and post-menopausal women.[30]
*Pre-menopausal women, more than 61 pg/mL; post-menopausal women, less than 60 pg/mL.
†Pre-menopausal women, 11–526 pg/mL; post-menopausal women, less than 37 pg/mL.
‡Pregnant women, 49.2–375 ng/mL at 21–42 wk.
§Women aged 20–39 y, 0.06–2.5 pg/mL; women aged 40–59 y, 0.04–2.0 pg/mL.
‖Women, 16–120 nmol/L; men, 10–73 nmol/L.
¶Pre-menopausal women, 1.5–33.4 mIU/mL; post-menopausal women, 23–116.3 mIU/mL.
#Pre-menopausal women, 0.5–73.6 mIU/mL; post-menopausal women, 15.9–54.0 mIU/mL.
**$P < .001$.
††$P < .01$.

larger cortical gray matter (GM) volumes (GMV) than post-menopausal women without ET, especially in the amygdaloid-hippocampal complex and cerebral cortex. A similar study[10] suggested that ET is related to the retention of GMV in parietal, pre-frontal, and temporal cortices of post-menopausal women. However, the studies mentioned above did not report a direct relationship between the level of estrogen and GMV change.

Aging process is also important in brain volume loss, with age-related structural brain studies[11,12] frequently describing a negative relationship between age and GMV. At least 1 study[13] examining brain volume and age in post-menopausal women focused on the hippocampus, finding a significant hippocampal volume reduction. Brain volume may vary as a function of time since menopause, because estrogen levels decline rapidly during menopause, and its receptors demonstrate reduced sensitivity over time in the absence of hormone exposure.[14] Therefore, it is imperative that more research be conducted to clarify how the brain volume in post-menopausal women changes with the level of specific hormone or aging.

A recently developed VBM technique, diffeomorphic anatomical registration through an exponentiated lie algebra (DARTEL), has grown in popularity since its introduction because of its more accurate inter-subject alignment in connection with image segmentation and registration than other VBM techniques.[15–17] To date, there has been no VBM study using the DARTEL algorithm assessing the correlation between brain volume alterations and sex hormone levels in post-menopausal women. DARTEL-based VBM of the whole cortex and associated areas (eg, the hippocampus and amygdala) will provide more accurate and valuable information on brain volume changes related specifically to the effects of menopause.

This study evaluated brain volume alterations in GM between pre-menopausal and post-menopausal women using DARTEL-based VBM; furthermore, it assessed the correlation between regional brain volume variations and sex hormone levels.

## METHODS

### Subjects

Along with 20 pre-menopausal women (mean age: 39.9 ± 8.1 years), 20 post-menopausal women (mean age: 55.7 ± 2.4 years) participated. Recruiting for the participants was done through advertisements.

A total of 20 pre-menopausal women were selected by the following criteria. First, they did not meet the menopause diagnosis based on the stages of reproductive aging workshop +10 and the regularity of menstrual bleeding. Second was the ovulation day estimated by the calendar or rhythm method. Third was no history of peri-menopause. Fourth was women without psychiatric and neurological illnesses. Fifth was no history of hormone and steroid treatment or oral contraception for 1 month before our study. A total of 20 post-menopausal women were chosen based on the following criteria. First, a menopause diagnosis based on the stages of reproductive aging workshop +10 and the regularity of menstrual bleeding. Second, greater than 30 μg/mL follicle-stimulating hormone (FSH) levels. Third, more than 1 year since last menstrual period. Fourth, no history of a hysterectomy/bilateral oophorectomy or psychiatric/neurological illnesses. Fifth, no history of hormone and steroid treatment or oral contraception for 1 month before our study. The average period after menopause in post-menopausal women was 5.5 ± 2.5 years. All volunteers

**Table 2.** Differential intracranial component volumes in pre-menopausal and post-menopausal women

| Tissue | Pre-menopausal women (n = 20) | Post-menopausal women (n = 20) | *P* value |
|---|---|---|---|
| Gray matter | 641.5 ± 24.4 $mm^3$ | 574.5 ± 38.0 $mm^3$ | .001* |
| White matter | 484.7 ± 42.0 $mm^3$ | 455.0 ± 49.0 $mm^3$ | .043† |
| Cerebrospinal fluid | 399.6 ± 78.7 $mm^3$ | 488.5 ± 136.0 $mm^3$ | .841 |
| Total volume | 1525.8 ± 112.2 $mm^3$ | 1517.9 ± 183.3 $mm^3$ | .203 |

*P* value was calculated by analysis of covariance with covariates of age.
*$P < .01$.
†$P < .05$.

received the experimental procedure and provided their written informed consent. This study was approved by the institutional review board of our hospital.

## Sex Hormones

The levels of the following serum sex hormones were measured: total estrogen, estradiol (E2), estriol, free testosterone, FSH, luteinizing hormone (LH), and SHBG.

The levels of total estrogen, estriol, free testosterone, and SHBG were measured by radioimmunoassay using a gamma counter (Cobra 5010 Quantum, Packard Instrument Co, Meriden, CT). The hormone blood test kits of total estrogen, E2, free testosterone, and SHBG were as follows: total estrogen (ICN Biomedicals Inc, Costa Mesa, CA), ESTRIOLO total radioimmunoassay coated tube (RADIM Diagnostics, Rome, Italy), Coat-A-Count free testosterone (Siemens Medical Solution Diagnostics, Los Angeles, CA), and IRMA-Count SHBG (Siemens Medical Solution Diagnostics Ltd, Caernarfon, United Kingdom).

The levels of E2, FSH, and LH were measured by chemiluminescent immunoassay using ADVIA Centaur System (Bayer Healthcare, Chicago, IL). The following test kits were used: ADVIA Centaur E2 chemiluminoimmunoassay kit (Bayer Healthcare LLC, New York, NY), ADVIA Centaur FSH (Bayer Healthcare LLC), and ADVIA Centaur LH (Bayer Healthcare LLC).

## MRI Acquisition

MRI was performed on a 3.0-T Magnetom Tim Trio MR scanner (Siemens Medical Solutions, Erlangen, Germany) with an 8-channel receiver head coil of birdcage type. The T1-weighted sagittal images were acquired using a 3-dimensional magnetization-prepared rapid-acquisition gradient echo pulse sequence with a repetition time/echo time = 1,900 ms/2.35 ms, field of view = 256 × 256 $mm^2$, matrix = 256 × 256, voxel size = 1 × 1 × 1 $mm^3$, and slices = 176.

## Structural Image Analyses

The T1-weighted images were post-processed using DARTEL-based VBM conducted using SPM 8 (Wellcome Department of Cognitive Neurology, University College London, London, United Kingdom). Prior to data processing, the images of the 40 women were aligned with an anterior—posterior commissure line. After correction of bias in the images due to field non-uniformity, MRI data were segmented into GM, white matter, and cerebrospinal fluid (CSF) using tissue probability maps based on the International Consortium of Brain Mapping space template for the East Asian brain type. The mean template for GM was created using individual GM images. All the images were normalized to the Montreal Neurological Institute template and were subsequently separated into GM images. Finally, all GM images were smoothed with the 8-mm full width at half maximum isotropic gaussian kernel. The total intracranial volume was measured by calculating the volumes of GM, white matter, and CSF in each woman.

A 2-sample *t* test ($P < .05$, family-wise error-corrected) and analysis of covariance (ANCOVA) adjusting for age were used to compare GMV between pre-menopausal and post-menopausal women. The cluster size included more than 50 contiguous voxels. A partial correlation adjusting for age was used to evaluate the correlation between the levels of sexual hormones and mean GMV in each brain area. In addition, the correlations between either age or period after menopause and mean GMV in each brain area were analyzed using Spearman correlation test. Each brain area's mask was applied to the evaluation of the mean GMV value. Which was calculated using the following equation:

$$\text{Mean GMV value} = \frac{\text{Sum of GMV value in total voxels}}{\text{total number of voxels in a given brain area}} \times 100$$

# RESULTS

## Levels of Sex Hormones

There were significant differences in the average levels of estrogen ($P < .001$), E2 ($P < .001$), FSH ($P < .001$), and LH ($P = .006$) between 2 groups (Table 1). However, there was no significant difference in estriol ($P = .554$), free testosterone ($P = .971$), or SHBG ($P = .051$) between the 2 groups.

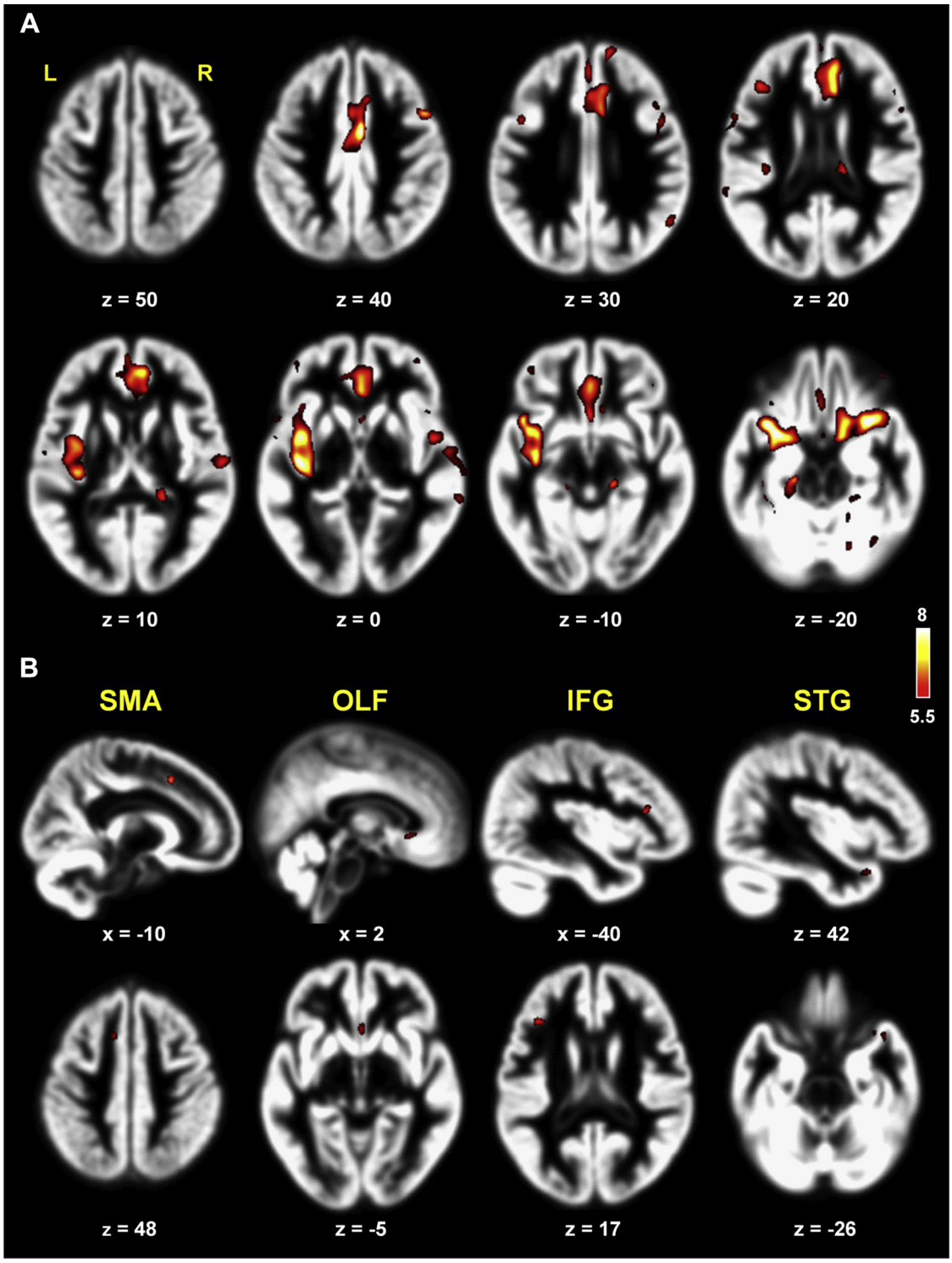


**Figure 1.** Brain areas with decreased gray matter volumes in post-menopausal women relative to pre-menopausal women: 2-sample *t* test (A) and analysis of covariance adjusting for age (B). The color-coded pixels were scaled to the range (*t* value) more than the cut-off threshold ($P < .05$). IFG = inferior frontal gyrus; L = left; OLF = olfactory cortex; R = right; SMA = supplementary motor area; STG = superior temporal gyrus.

## Intracranial Component Volume

The GMV of pre-menopausal and post-menopausal women were 641.5 ± 24.4 mL and 574.5 ± 38.0 mL ($P < .001$), respectively, and the white matter volumes were 484.7 ± 42.0 mL and 455.0 ± 49.0 mL ($P = .043$), respectively (Table 2). The CSF volumes of pre-menopausal and post-menopausal women were 399.6 ± 78.7 mL and 488.5 ± 136.0 mL, respectively ($P < .841$); total intracranial volumes were 1525.8 ± 112.2 mL and

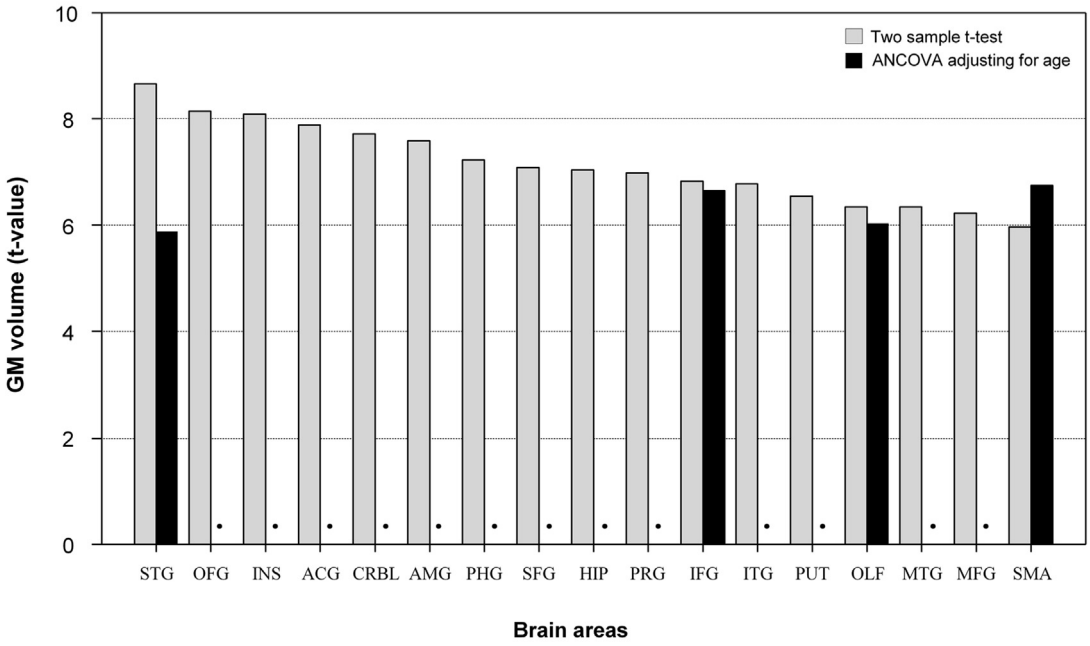


**Figure 2.** Gray matter (GM) volume (maximum *t* value) observed in pre-menopausal women relative to menopausal women: 2-sample *t* test and analysis of covariance (ANCOVA) adjusting for age ($P < .05$). ACG = anterior cingulate gyrus; AMG = amygdala; CRBL = cerebellar cortex; HIP = hippocampus; IFG = inferior frontal gyrus; INS = insula; ITG = inferior temporal gyrus; MFG = middle frontal gyrus; MTG = middle temporal gyrus; OFG = orbitofrontal gyrus; OLF = olfactory cortex; PHG = parahippocampal gyrus; PRG = pre-central gyrus; PUT = putamen; SFG = superior frontal gyrus; SMA = supplementary motor area; STG = superior temporal gyrus.

1517.9 ± 183.3 mL ($P = .203$). The volumes of CSF and total intracranial volume were not significantly different.

## GMV Alteration

Figure 1 shows brain areas with reduced GMV in post-menopausal women as contrasted with pre-menopausal women.

Post-menopausal women showed significantly lower GMV in the superior temporal gyrus (STG), orbitofrontal gyrus, insula, anterior cingulate gyrus, cerebellar cortex, amygdala, parahippocampal gyrus, superior frontal gyrus, hippocampus, pre-central gyrus, inferior frontal gyrus (IFG), inferior temporal gyrus, putamen, olfactory cortex (OLF), middle temporal gyrus, middle frontal gyrus, and supplementary motor area (SMA) compared with the pre-menopausal women using 2-sample *t* test ($P < .05$) (Figures 1 and 2, and Table 3). In the between-groups ANCOVA ($P < .05$), post-menopausal women showed significantly reduced GMV of the SMA, IFG, OLF, and STG (Figures 1 and 2, and Table 3).

## Correlation of GMV With Age or Period After Menopause

Ages in women were negatively correlated with GMV values in the orbitofrontal gyrus ($\rho = -0.63$, $P < .001$), insula ($\rho = -0.72$, $P < .001$), anterior cingulate gyrus ($\rho = -0.74$, $P < .001$), cerebellar cortex ($\rho = -0.61$, $P < .001$), amygdala ($\rho = -0.52$, $P = .001$), parahippocampal gyrus ($\rho = -0.49$, $P = .001$), superior frontal gyrus ($\rho = -0.61$, $P < .001$), hippocampus ($\rho = -0.50$, $P = .001$), pre-central gyrus ($\rho = -0.54$, $P < .001$), inferior temporal gyrus ($\rho = -0.53$, $P < .001$), putamen ($\rho = -0.42$, $P = .007$), middle temporal gyrus ($\rho = -0.52$, $P = .001$), and middle frontal gyrus ($\rho = -0.64$, $P < .001$) (Figure 3). In addition, periods after menopause were negatively correlated with the GMV values in the SMA of post-menopausal women ($\rho = -0.47$, $P = .035$) (Figure 4).

## Correlation of GMV With Sex Hormones

Table 4 shows the correlations between the GMV values and the sex hormones in women. The levels of estrogen were positively correlated with the GMV values of the SMA ($\gamma = 0.46$, $P = .003$), OLF ($\gamma = 0.36$, $P = .027$), and STG ($\gamma = 0.36$, $P = .023$); those of E2 were positively correlated with the GMV values of the SMA ($\gamma = 0.42$, $P = .007$), IFG ($\gamma = 0.35$, $P = .030$), and STG ($\gamma = 0.42$, $P = .008$); and those of FSH were negatively correlated with the GMV values of the SMA ($\gamma = -0.48$, $P = .002$), IFG ($\gamma = -0.48$, $P = .002$), OLF ($\gamma = -0.46$, $P = .003$), and STG ($\gamma = -0.51$, $P = .001$). The levels of SHBG were positively correlated with the GMV values of the STG ($\gamma = 0.33$, $P = .040$).

## DISCUSSION

To our understanding, this represents the first research in assessing volumetric changes on GM in post-menopausal women using DARTEL-based VBM, and their correlations with sex hormone levels. Total GMV in post-menopausal women were

**Table 3.** Differential intracranial component volumes in pre-menopausal and post-menopausal women

| Brain areas | *t* Value | Montreal Neurological Institute coordinates | | | Voxels, n | FWE-corrected *P* |
|---|---|---|---|---|---|---|
| | | x | y | z | | |
| 2-Sample *t* test | | | | | | |
| Superior temporal gyrus | 8.66 | −30 | 9 | −22 | 1,813 | .000* |
| Orbitofrontal gyrus | 8.15 | 31 | 17 | −21 | 1,970 | .000* |
| Insula | 8.09 | −39 | 4 | −5 | 6,487 | .000* |
| Anterior cingulate gyrus | 7.89 | 9 | 34 | 18 | 4,243 | .000* |
| Cerebellar cortex | 7.72 | −41 | −47 | −29 | 4,313 | .000* |
| Amygdala | 7.59 | −30 | 8 | −22 | 653 | .000* |
| Parahippocampal gyrus | 7.23 | −24 | 9 | −24 | 579 | .001† |
| Superior frontal gyrus | 7.09 | 7 | 49 | 8 | 4,506 | .001† |
| Hippocampus | 7.04 | −19 | −23 | −15 | 51 | .001† |
| Pre-central gyrus | 6.99 | 50 | 11 | 40 | 246 | .001† |
| Inferior frontal gyrus | 6.83 | 47 | 13 | 38 | 665 | .002† |
| Inferior temporal gyrus | 6.78 | 32 | 4 | −42 | 494 | .002† |
| Putamen | 6.55 | −33 | −9 | 0 | 395 | .003† |
| Olfactory cortex | 6.35 | 1 | 19 | −9 | 461 | .006† |
| Middle temporal gyrus | 6.35 | 36 | 17 | −39 | 485 | .006† |
| Middle frontal gyrus | 6.23 | 48 | 12 | 41 | 291 | .008† |
| Supplementary motor area | 5.97 | 6 | 2 | 43 | 734 | .017‡ |
| ANCOVA adjusting for age | | | | | | |
| Supplementary motor area | 6.75 | −11 | 16 | 45 | 190 | .002† |
| Inferior frontal gyrus | 6.65 | −39 | 27 | 15 | 166 | .003† |
| Olfactory cortex | 6.04 | 1 | 23 | −5 | 108 | .015‡ |
| Superior temporal gyrus | 5.89 | 42 | 17 | −26 | 53 | .022‡ |

*P* value was calculated by 2-sample *t* test and ANCOVA with covariates of age.
ANCOVA = analysis of covariance.
*$P < .001$.
†$P < .01$.
‡$P < .05$.

lower compared to menopausal women, particularly in SMA, IFG, OLF, and STG. Interestingly, the GMV values of SMA, IFG, and STG were positively correlated with the levels of E2, whereas that of the SMA was negatively correlated with the duration of time after menopause in post-menopausal women.

A previous morphological study[13] evaluating the effect of aging in post-menopausal women reported that the reduced hippocampal volume observed is closely associated with age-related structural change; this finding is consistent with our result that post-menopausal women showed reduced GMV in the hippocampus with ANCOVA not adjusted for age. Several studies[7,9,10] assessing ET suggested that increased estrogen either ameliorates or has a neutral effect on the structural integrity of neural tissue, especially in the pre-frontal, temporal, and parietal lobes. E2 levels of post-menopausal women in our study were significantly lower than those in pre-menopausal women, as would be expected; in contrast, FSH was significantly higher. The production of estrogen declines with age and overlaps with the transition to menopause; greater production has positive effects on cognition, neuroprotection, and related brain characteristics.[18] ET may influence clinical outcomes through vascular changes or effects on regional brain volumes, including neuronal architecture and synaptic density.[14]

The decrease in local GMV seen in our study could be associated with cell loss or/and cell shrinkage related to hormone loss. Post-menopausal women showed reduced GMV in the SMA, IFG, OLF, and STG, all of which are related to cognitive function. Estrogen receptors were localized to the frontal cortex, including the primary OLF. The SMA, IFG, and OLF may thus be amenable to neuroprotection by estrogens. In addition, there is evidence that estrogen stimulates a significant increase in the density of 5-hydroxytryptamine 2A binding sites in anterior frontal and OLF.[19]

Acute ovarian suppression in healthy young women as well as the use of estrogen treatment in post-menopausal women can modulate membrane turnover in brain regions critical to memory.[7,20,21] A similar study[22] concerning sex hormones suggested that estrogen and E2 considerably improved verbal memory by enhancing verbal information processing and decreasing forgetfulness. In fact, the IFG has previously been reported to be more vulnerable than other cortical regions to E2-related volume increases.[23] Interestingly, a positron emission

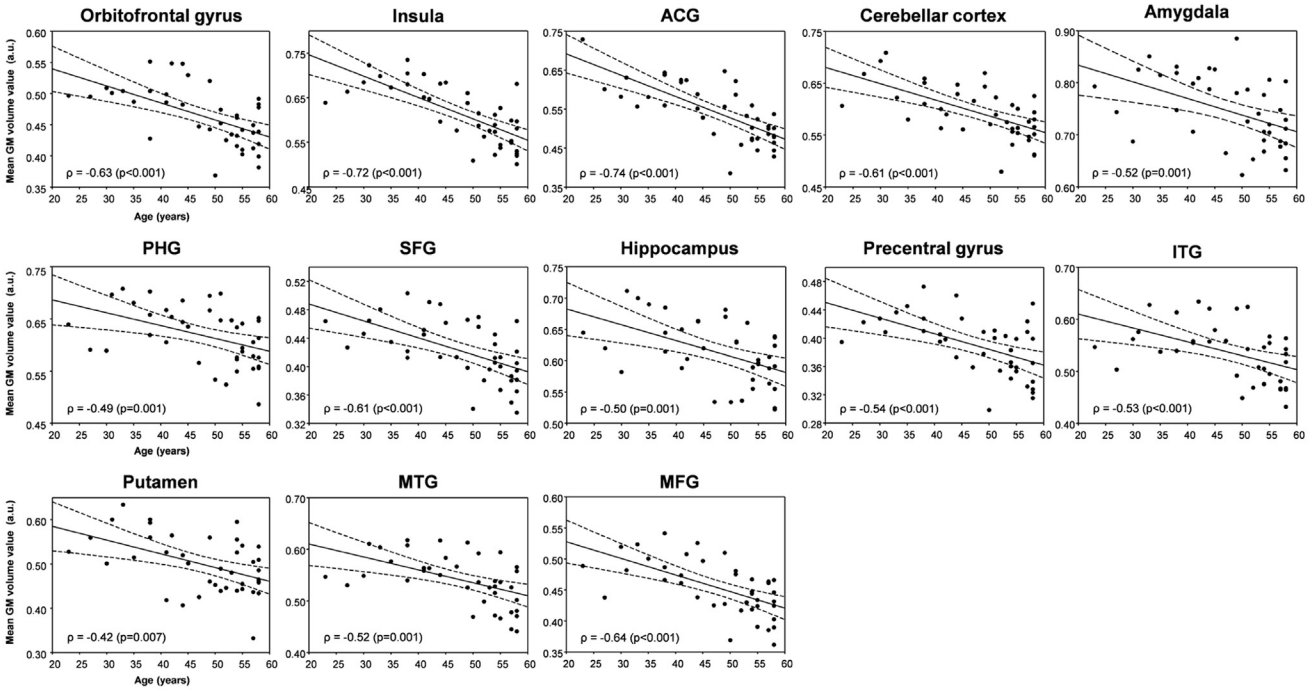


**Figure 3.** Ages in women were negatively correlated with mean gray matter (GM) volume value in the orbitofrontal gyrus, insula, anterior cingulate gyrus (ACG), cerebellar cortex, amygdala, parahippocampal gyrus (PHG), superior frontal gyrus (SFG), hippocampus, pre-central gyrus, inferior temporal gyrus (ITG), putamen, middle temporal gyrus (MTG), and middle frontal gyrus (MFG). Dotted lines show 95% CI. a.u. = arbitrary unit.

tomography study[3] reported that the accumulation of time of endogenous estrogen exposure was positively correlated with cerebral metabolism in the IFG in post-menopausal women receiving ET. In addition, post-menopausal women receiving ET showed greater GMV in the IFG than did post-menopausal women who were no longer receiving ET.[9] The OLF is situated at the base of the frontal lobe and the medial aspect of the temporal lobe, and is involved in olfaction.[24] This area is significantly altered in old age and in a number of age-related diseases.[25] Doty et al[26] revealed improved olfactory and cognitive function after estrogen treatment in post-menopausal women, consistent with our finding that the GMV of the OLF was positively correlated with the levels of estrogen. Moreover, we demonstrated the negative correlation of the GMV values of the SMA with the duration of time after menopause. Notably, estrogen loss may be largest in the frontal lobe associated with cognitive dysfunction.

In comparison to a previous morphological study,[9] the STG volumes of post-menopausal women were decreased. The STG has been implicated in language processing and social perception, and is widely recognized to be sensitive to estrogen changes.[27,28] A SPECT study[28] with the radiotracer [123I] iodobenzovesamicol reported vesicular acetylcholine transporter binding indices in post-menopausal women receiving ET were positively correlated with the number of years of hormone replacement in the frontal and temporal cortices. Dumas et al[29] noted that post-menopausal women receiving ET showed greater activation in the STG in the 0-back task using functional MRI, while a fluorodeoxyglucose—positron emission tomography study[27] demonstrated that subjects treated with estrogen showed larger increases in relative cerebral blood flow of the STG during both the resting condition and a verbal activation task. In addition, years of estrogen exposure tended to positively correlate with metabolism in the STG.[3] The levels of estrogen and E2 in our study were positively correlated with the GMV values of

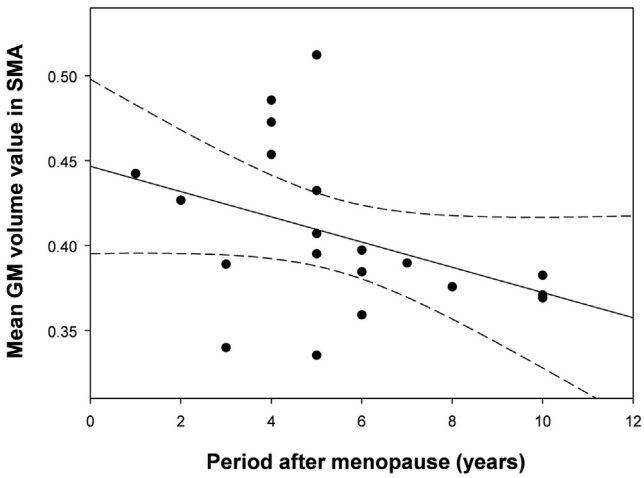


**Figure 4.** Mean gray matter (GM) volume value of the supplementary motor area (SMA) in post-menopausal women was negatively correlated with period after menopause. Dotted lines show 95% CI.

**Table 4.** Correlations between mean gray matter volume values and sex hormones in women

| Sex hormones | SMA | IFG | OLF | STG |
|---|---|---|---|---|
| Total estrogen, pg/mL | 0.46 (.003*) | 0.30 (0.060) | 0.36 (0.027†) | 0.36 (0.023†) |
| Estradiol, pg/mL | 0.42 (0.007*) | 0.35 (0.030†) | 0.27 (0.091) | 0.42 (0.008*) |
| Estriol, pg/mL | −0.16 (0.921) | −0.23 (0.166) | −0.23 (0.163) | −0.19 (0.243) |
| Free testosterone, pg/mL | 0.05 (0.771) | −0.09 (0.589) | 0.11 (0.506) | 0.00 (0.979) |
| SHBG, nmol/L | 0.30 (0.065) | 0.29 (0.076) | 0.09 (0.577) | 0.33 (0.040†) |
| Follicle-stimulating hormone, mIU/mL | −0.48 (0.002*) | −0.48 (0.002*) | 0.46 (0.003*) | −0.51 (0.001*) |
| Luteinizing hormone, mIU/mL | −0.03 (0.849) | −0.07 (0.652) | −0.04 (0.803) | −0.09 (0.588) |

Data are presented as $\gamma$ ($P$).
$P$ value was calculated by partial correlation adjusting for age.
IFG = inferior frontal gyrus; OLF = olfactory cortex; SMA = supplementary motor area; STG = superior temporal gyrus.
*$P < .01$.
†$P < .05$.

the STG. This may help explain the underlying estrogen-related morphometric changes in post-menopausal women. The reduced GMV of the STG in post-menopausal women is likely to be because of the decrease in E2 following menopause.

There are some limitations in this study. First, the population of subjects was small. Second, sex hormones and aging are both important factors in brain volume loss in post-menopausal women that may interact. To evaluate age- and estrogen-related morphometric changes, we directly compared pre-menopausal and post-menopausal women; however, they were un-matched for age. Further study of pre-menopausal and post-menopausal women matched by age, particularly with the addition of diffusion tensor imaging, might be helpful to assess menopause-related morphometric alterations. Third, estrogen has a protective role in cognitive decline, but we did not measure cognitive function using intelligence quotient, the Mini-Mental State Examination, or other intelligence tests. In spite of such limitations, we demonstrated estrogen-related morphometric changes in specific brain areas, suggesting a neuroprotective effect of estrogen in the cortex.

## CONCLUSION

This study compared the differential GMV variations over whole brain structures between pre-menopausal and post-menopausal women using DARTEL-based VBM, as well as their correlations with sex hormones. It is potentially considered that volumetric abnormality of the SMA, IFG, OLF, and STG is associated with the brain function in post-menopausal women. These findings are potentially helpful to understand the brain function that may be associated with morphological changes specific to menopause.

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### Category 3

**(a) Final Approval of the Completed Article**
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