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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