WOMEN'S SEXUAL HEALTH

Brain Morphological Changes With Functional Deficit Associated With Sexual Arousal in Postmenopausal Women

Han-Su Baek, PhD,[1] Gwang-Won Kim, PhD,[2] Thirunavukkarasu Sundaram, PhD,[3] Kwangsung Park, PhD, MD,[2,4] and Gwang-Woo Jeong, PhD, MPh[1]

ABSTRACT

Introduction: We have not known how menopause synchronously influences brain morphology and function associated with visually stimulated sexual arousal in postmenopausal women.

Aim: This study used a combination of functional magnetic resonance imaging and voxel-based morphometry to evaluate menopause-related brain morphological and functional changes in postmenopausal women.

Methods: Nineteen premenopausal women and 19 postmenopausal women underwent functional and structural magnetic resonance imaging. Brain function activity was measured while the subjects viewed an erotic video clip.

Main Outcome Measures: A 2-sample *t*-test was used for cross-analysis of the 2 groups for comparison of gray matter volumes (corrected $P < .05$) and brain activation (uncorrected $P < .01$).

Results: Our study revealed a relationship between sexual function and morphological changes in postmenopausal women. Compared with premenopausal women, the postmenopausal group showed significantly lower brain activations in the major parts of the limbic system and basal ganglia, including the parahippocampal gyrus, head of caudate nucleus, insula, putamen, hippocampus, hypothalamus, amygdala, and globus pallidus, which are involved in sexual behavior and emotional responses. In morphometric analyses, postmenopausal women showed significantly decreased gray matter volumes of the insula, putamen, parahippocampal gyrus, amygdala, and anterior cingulate gyrus, most of which were associated with decreased functional activity during visual sexual arousal in postmenopausal women. In addition, the premenopausal group alone showed a positive correlation between the activity of the insula and the level of estradiol (Pearson correlation $r = 0.588$; $P = .008$).

Conclusion: This study demonstrates an association between menopause-related brain function and morphological changes in postmenopausal women. This finding provides insight into the neural mechanisms associated with the sexual functional deficit in postmenopausal women. **Baek H-S, Kim G-W, Sundaram T, et al. Brain Morphological Changes with Functional Deficit Associated with Sexual Arousal in Postmenopausal Women. Sex Med 2019;7:480–488.**

Key Words: Brain Activation; Gray Matter; Postmenopausal Women; Sexual Arousal

Received December 25, 2018. Accepted June 25, 2019.

[1]Department of Radiology, Chonnam National University Hospital, Chonnam National University Medical School, Gwangju, Republic of Korea;

[2]Advanced Institute of Aging Science, Chonnam National University, Gwangju, Republic of Korea;

[3]Department of Radiology, Rajah Muthiah Medical College Hospital, Annamalai University, Chidambaram, India;

[4]Department of Urology, Chonnam National University Hospital, Chonnam National University Medical School, Gwangju, Republic of Korea

https://doi.org/10.1016/j.esxm.2019.06.013

INTRODUCTION

Menopause is defined as the permanent cessation of menstruation in women due to decreased functioning of the ovarian follicle with aging, and it represents a natural end to a woman's reproductive years.[1,2] Reproductive stages in women can be divided based on the final menstrual period, and the postmenopausal period refers to the absence of actual menstrual cycle, with natural amenorrhea lasting 12 months or more.[3]

A common problem in an aging society is decreased sexual function in postmenopausal women. A decrease in estrogen production in menopausal women leads to epithelial thinning and reduced lubrication of the genitalia during sexual arousal.[4] In about

45% of menopausal women, vaginal atrophy clinically manifests as a syndrome of vaginal dryness, itching, irritation, and dyspareunia.[5] Several studies[2,6,7] have reported diminished sexual desire and interest in postmenopausal women, as well as decreased sexual responsiveness. The effects of estrogen on brain structure have seldom been investigated using functional magnetic resonance imaging (fMRI) and voxel-based morphometry (VBM). A morphological study[8] reported a significant reduction in hippocampal volume of postmenopausal women compared with premenopausal women. A VBM study[9] that focused on the comparative effects of treatment with and without hormones found that menopausal women receiving estrogen therapy showed greater gray matter (GM) volumes, especially involving the amygdaloid-hippocampal complex and frontal, temporal, parietal, and occipital cortices. Kim and Jeong[4] reported that the blood-oxygen-level-dependent signal changes in the amygdala of women watching erotic videos were positively correlated with estrogen levels in women.

Sexual dysfunction in postmenopausal women is 2.3-fold higher compared with premenopausal women.[10] A meta-analysis of menopause-related sexual dysfunction worldwide reported that approximately 60% of women ages 40 to 64 years experienced sexual dysfunction; for example, the rate was 82.3% (on average) in Australia (2002-2011), 69.8% in South America (2003-2013), 63.5% in Asia (2002-2013), 60.3% in Africa (2009-2012), 54.5% in Europe (2007-2013), and 32.0% in North America (2006-2013).[11] A study correlating declining sexual function with activation of the central nervous system in postmenopausal women would be important for better understanding the neural mechanisms underlying the differences in sexual function associated with menopause.[12-15]

Most of the neuroimaging techniques evaluating sexual arousal in humans include fMRI and positron emission tomography.[16-20] Park et al[21] reported that the brain centers associated with visual sexual arousal in women include cingulate gyrus, insula, thalamus, and caudate nucleus. Bartels and Zeki[16] demonstrated significantly increased activities in the insula, anterior cingulate cortex, caudate nucleus, and putamen of healthy subjects viewing pictures of their loved partners and friends. Maravilla and Yang[22,23] reviewed the utility of fMRI as a tool in assessing female sexual function in combination with clinical perspectives. Jeong et al[14] investigated declining sexual function following menopause in relation to brain activation in premenopausal and postmenopausal women. An excellent study[24] reporting the differential brain response to menstrual cycle in premenopausal women revealed that the dominant brain activation in response to sexual stimuli peaked in the mid-luteal phase, especially in areas such as the anterior cingulate gyrus, insula, and orbitofrontal gyrus. Another interesting study[25] used fMRI to establish a correlation between hot flashes, one of the most representative menopausal symptoms in postmenopausal women, and brain activation. The study revealed that hot flashes were related to activation of the insula and the anterior cingulate gyrus, which control the thermoregulatory mechanism. The studies mentioned above did not investigate the association between brain morphology and functional deficits.

Here, we assumed that morphometric and functional deficits are closely related to each other, and the combined results provide important insight into the hyposexuality of postmenopausal women. Using fMRI and VBM, this study explored functional and morphological variation in the brains of women.

MATERIALS AND METHODS

Subjects

Nineteen premenopausal (40.2 ± 6.7 years) and 19 postmenopausal (55.5 ± 2.6 years) women without brain dysfunction or a history of reproductive surgery participated in this study. All of the women were recruited via advertisements. None of the women had used any oral contraceptive, other hormone treatment, or steroidal drugs during the period at least 1 month prior to the experiment. Of the 19 premenopausal women, 17 were married and had 1.8 ± 1.0 children, and 2 were single. All of the 19 postmenopausal women were married and had 2.8 ± 0.7 children (Table 1). Of the 19 premenopausal women, 7 described their religion as Buddhist, 3 as non-Catholic Christian, and 2 as Catholic; 7 claimed no religion. In the postmenopausal group, 9 were Buddhists, 4 were non-Catholic Christians, and 4 were Catholics; only 2 claimed not to follow any designated religion (Table 1).

Assigning subjects into the premenopausal group or the postmenopausal group was based on natural amenorrhea or cessation of the menstrual cycle for at least 1 year or more and blood follicle-stimulating hormone (FSH) levels of 40.0 mIU/mL. Prior to the experiment, all of the experimental procedures were explained to them and the written informed consent was obtained. All of the experimental protocols were approved by our hospital internal review board (I-2008-05-065).

Table 1. Demographic characteristics of the pre- and postmenopausal women

Demographic	Premenopausal women (n = 19)	Postmenopausal women (n = 19)
Age (y), mean ± SD	40.2 ± 6.7	55.5 ± 2.6
Number of children, mean ± SD	1.8 ± 1.0	2.8 ± 0.7
Academic level, n		
Primary	0	5
Secondary	4	13
University	15	1
Marital status, n		
Married	17	19
Single	2	0
Religion, n		
Buddhism	7	9
Catholic	2	4
Non-Catholic Christian	3	4
No religion	7	2

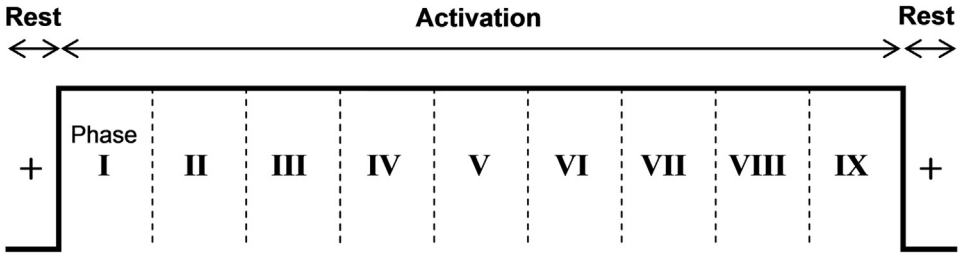

Figure 1. Activation paradigm for the time course of sexual arousal, consisting of a series of 9 segments of 1-minute duration each.

Measurement of Serum Sex Hormone Concentrations

The venous blood samples of the forearm were obtained via routine vein puncture. The levels of estrogen, estriol, free testosterone (T), and sex hormone-binding globulin were measured using radioimmunoassay, and the levels of luteinizing hormone (LH), FSH, and estradiol were measured using chemiluminescence immunoassay. Statistical analysis (2-sample *t*-test) of the hormone levels was performed using SPSS 19.0 (IBM; Armonk, NY).

Assessment of Female Sexual Function Index

For objective measurement of sexual functioning in the subjects, the Korean version of the Female Sexual Function Index (FSFI) was used.[26] We conducted a 2-tier analysis of scores in each of the 6 domains and the total FSFI score using questionnaires completed by the pre- and postmenopausal groups. In addition, the correlation between the subjects' age and FSFI score was statistically analyzed.

Visual Stimuli and Procedure

The test procedure consisted of a rest phase for 30 seconds, an activation phase for 9 minutes, and a rest phase for 30 seconds (Figure 1). During the rest phase, subjects were asked to stare at a screen with a gray background and a white cross in the middle and to remain focused. During the activation phase, an erotic video consisting of consecutive sexual stimuli (caressing, fellatio, and cunnilingus between a man and a woman) was presented. The subjective response to the video footage presented during the fMRI experiment was assessed on the basis of a scale of 7 (0-6) for 3 domains: attention, interest, and sexual arousal. In addition, the video footage presented during the activation phase for 9 minutes was shown again right after the experiment to select the time interval with the highest degree of sexual arousal in each subject. The fMRI raw data acquired during the time phase with the highest sexual arousal was extracted for post-processing the fMRI images.

MRI and fMRI Acquisition

The fMRI and T1-weighted images were acquired using a MAGNETOM Trio 3.0T MRI Scanner (Siemens Healthineers; Munich, Germany) and a standard birdcage-type head coil. To induce images of brain activation, the erotic videos were projected through a semitransparent screen to facilitate viewing through a mirror. The fMRI pulse sequence was gradient-echo echo-planar imaging with the following characteristics: repetition time/time to echo (2000/30 msec), field of view (22 cm × 22 cm), matrix (64 × 64), number of slices (30), slice thickness (5 mm), flip angle (90°0), and slice interval (0 mm). Each slice image was acquired from the axial plane parallel to the anterior commissure-posterior commissure line. The pulse sequence of the T1-weighted images was based on a multiplanar rapidly acquired gradient echo with the following characteristics: repetition time/time to echo (1900/2.35 msec), matrix (256 × 256), and field of view (22 cm × 22 cm).

MRI and fMRI Analyses

T1-weighted and fMR images were post-processed using SPM software. All of the T1 images in the 38 women were aligned with the anterior commissure-posterior commissure line. The Montreal Neurological Institute template was used to normalize the individual GM images, which were modulated.[27] A Gaussian kernel of 8 mm full width at half maximum was used to smooth the GM images. In order to compare GM volumes between the 2 groups, a 2-sample *t*-test ($P < .05$, family-wise error) was performed. During functional imaging, the 9-minute activation phase was divided into 9 segments of 1 minute each. Among the 9 segments, a single 1-minute segment that included the maximal sexual arousal based on the follow-up questionnaire was selected for post-processing (Figure 1).

Movements of subjects with a gap exceeding ±2 mm of translation or ±2° of rotation during image acquisition may induce serious artifacts in fMRI images; therefore, a rigid body transformation was used to correct the subjects' movements by realigning the translation and the rotation between fMRI images. The individual data were normalized to the standard cerebral space, Montreal Neurological Institute coordinates, for the analysis of group-based findings. Finally, data grids of regular thick slices underwent a smoothing process of ungridding using a Gaussian kernel of 8 mm full width at half maximum. A sample *t*-test was used to analyze each group (uncorrected $P < .005$), whereas a 2-sample *t*-test was used for cross-comparison of the 2 groups (uncorrected $P < .01$). Pearson *t*-test was used to determine the association between the levels of sexual hormone and brain activation.

Overlapping activation map and standardized T1-weighted images were analyzed using MRIcron (Chris Rorden's Neuropsychology Lab; Columbia SC). The activation ratio of a specified brain area was calculated using the following equation:

$$\text{Activation ratio}(\%) = \frac{\text{Activated number of voxel in specified brain structure}}{\text{Total number of voxels in the specified brain structure}} \times 100$$

This activation ratio was used to ascertain the hemisphere dominance, and the term "activity" was used to represent the activation intensity, which is a voxel-based maximal t value in the corresponding brain area. Based on earlier fMRI studies,[14,16-18,20,21] we identified 11 brain regions of interest related to sexual arousal: head of caudate nucleus, globus pallidus, putamen, anterior cingulate gyrus, insula, thalamus, hypothalamus, hippocampus, amygdala, septal area, and parahippocampal gyrus.

RESULTS

Blood Sex Hormone Concentrations

The sex hormone levels of premenopausal and postmenopausal women based on the 2-sample t-test were as follows: average levels of estrogen, 541.1 ± 333.3 pg/mL and 79.1 ± 42.9 pg/mL ($P < .001$), respectively; estradiol levels, 209.2 ± 175.7 pg/mL and 13.6 ± 7.6 pg/mL ($P < .001$); FSH levels, 5.9 ± 4.0 mIU/mL and 68.9 ± 18.7 mIU/mL ($P < .001$); LH levels, 12.5 ± 13.5 mIU/mL and 38.9 ± 11.6 mIU/mL ($P < .001$); sex hormone-binding globulin levels, 103.1 ± 32.2 nmol/L and 69.5 ± 17.6 nmol/L ($P < .001$); free T levels, 0.4 ± 0.3 pg/mL and 0.3 ± 0.2 pg/mL ($P = .325$); and estriol levels, 3.0 ± 1.7 ng/mL and 2.5 ± 1.5 ng/mL ($P = .435$).

Assessment of FSFI Questionnaire

In the pre- and postmenopausal women, the average total FSFI scores were 25.5 ± 7.5 and 16.6 ± 9.7, respectively (2-sample t-test; $P = .001$); desire scores, 2.9 ± 1.1 and 2.5 ± 1.1 ($P = .349$); arousal scores, 4.1 ± 1.5 and 2.7 ± 2.0 ($P = .023$); lubrication scores, 4.9 ± 1.4 and 3.0 ± 2.3 ($P = .004$); orgasm scores, 4.4 ± 1.5 and 2.9 ± 2.1 ($P = .014$); satisfaction scores, 4.3 ± 1.5 and 3.0 ± 1.7 ($P = .012$); and pain scores, 5.0 ± 1.8 and 2.6 ± 2.4 ($P = .001$).

Brain Activation Induced by Visual Sexual Stimulation

In the pre- and postmenopausal women, the average scores for perceived sexual arousal following exposure to sexual stimuli were 3.5 ± 1.4 and 3.1 ± 1.6, respectively (2-sample t-test; $P = .538$); scores for interest in sexual stimuli, 3.7 ± 1.8 and 4.1 ± 1.4 ($P = .709$); and scores for attention to sexual stimuli, 4.3 ± 1.5 and 4.7 ± 0.9 ($P = .497$). During the 9-minute activation, the time slots with the highest sexual arousal were the sixth segment, which included vaginal intercourse (7/19 subjects in each premenopausal and postmenopausal group), and the third segment, which included oral sex scenes (5/19 subjects in the premenopausal and 4/19 subjects in the postmenopausal group), followed by the first segment, which included an undressing scene (4/19 subjects in each premenopausal and postmenopausal group). The brain activities and activation ratios were calculated from 1-minute segment data including the time slot with the highest sexual arousal in each subject ($P < .005$).

Figure 2 illustrates the hemisphere dominance in premenopausal (red color) and postmenopausal (green) women, as well as the overlapping brain areas (yellow) that were both activated in each group (1-sample t-test; uncorrected $P < .005$). As seen in Figure 2, the premenopausal women showed a marked activation in the septal area, insula, and thalamus, which were predominantly activated in the right hemisphere, as well as the head of caudate nucleus, parahippocampal gyrus, putamen, amygdala, globus pallidus, hypothalamus, and hippocampus, which showed left-hemisphere dominance. In contrast, the postmenopausal women showed marked activation in the parahippocampal gyrus, hippocampus, thalamus, septal area, insula, globus pallidus, and amygdala, which were predominantly activated in the right hemisphere, as well as the head of caudate nucleus and putamen, which showed left-hemisphere dominance.

Comparisons of Brain Activities and GM Volumes

Compared with the premenopausal group, the postmenopausal women showed lower activities in the following brain regions: parahippocampal gyrus, head of caudate nucleus, insula, putamen, hippocampus, hypothalamus, amygdala, and globus pallidus (Figure 3 and Table 2) (uncorrected $P < .01$). The postmenopausal women showed lower GM volumes in the insula, putamen, parahippocampal gyrus, amygdala, and anterior cingulate gyrus compared with premenopausal women (Figure 4 and Table 2) (corrected $P < .05$).

Relationships Between Sex Hormones and Brain Activities

The comparative analysis of the two groups based on sex hormone levels and intensity of brain activation in the 2 groups revealed a significant correlation only between estradiol levels and the activation intensity of the insula in premenopausal women (Pearson correlation $r = 0.588$; $P = .008$) (Figure 5).

DISCUSSION

In this study, estrogen ($P < .001$) and estradiol ($P < .001$) levels in premenopausal women were about 7- and 15-fold

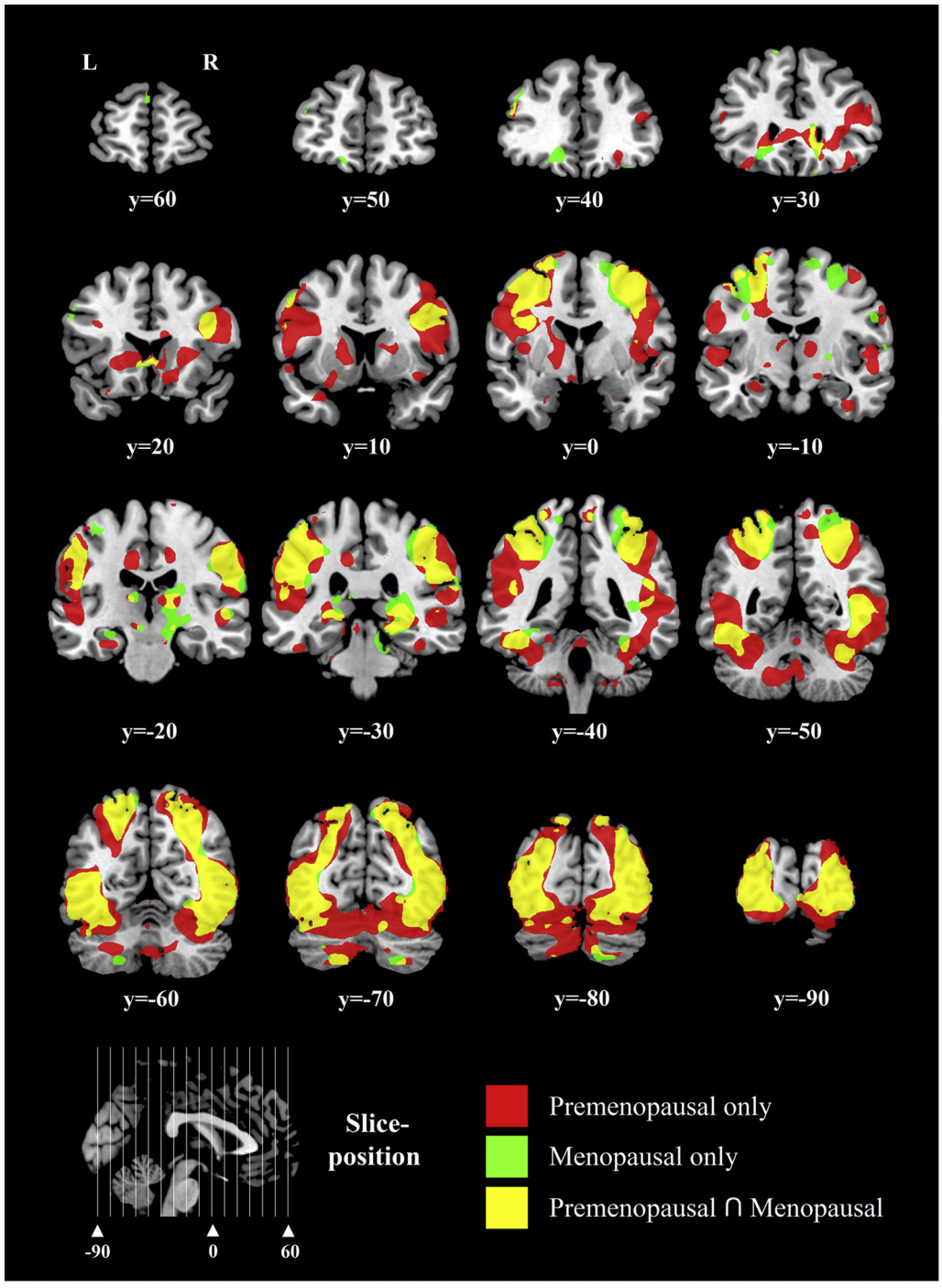

Figure 2. Brain activation maps in premenopausal (red) and menopausal (green) women. Overlapped activation areas of premenopausal and postmenopausal women are highlighted in yellow (1-sample *t*-test; uncorrected $P < .005$).

higher, respectively, compared with the postmenopausal group. However, the FSH ($P < .001$) and LH ($P < .001$) levels in postmenopausal women were 12-fold and 3-fold higher, respectively, than in the premenopausal group. The other sex hormones, including free T ($P = .325$) and estriol ($P = .435$), were not significantly divergent from each other in the 2 groups.

With regard to self-assessment of the 6 domain-based sexual functions in FSFI, the premenopausal and postmenopausal women scored 25.5 ± 7.5 and 16.6 ± 9.7 out of 36 points, respectively. Because the threshold score for sexual dysfunction in Korean women is 25 points, as defined by Song et al,[28] the postmenopausal women were assumed to be sexually dysfunctional physiologically and physically.

Another interesting finding of this study was the lack of significant difference between premenopausal and postmenopausal women based on their responses for the follow-up questionnaire on visual sexual stimulation in the fMRI experiment: attention ($P = .497$), interest ($P = .709$), and sexual arousal ($P = .538$).

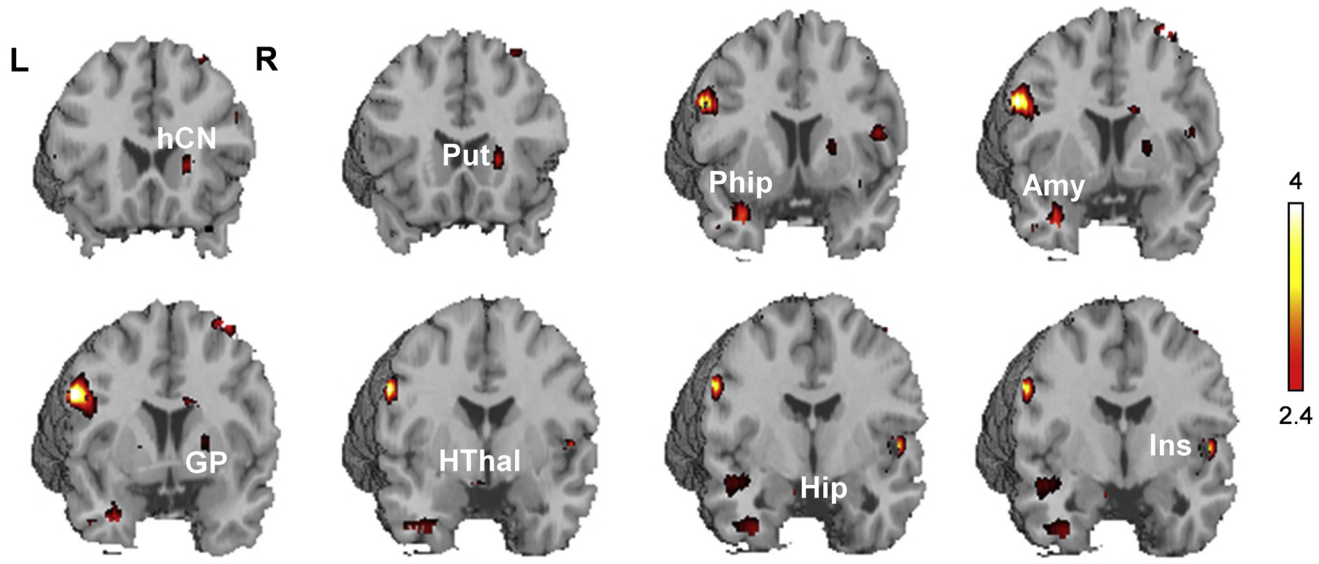

Figure 3. A series of color-coding activation maps in three dimensions demonstrating the predominantly activated areas in premenopausal vs postmenopausal women (uncorrected $P < .01$). Amy = amygdala; GP = globus pallidus; hCN = head of caudate nucleus; Hip = hippocampus; HThal = hypothalamus; Ins = insula; Phip = parahippocampal gyrus; Put = putamen.

However, postmenopausal women showed lower activations involving the parahippocampal gyrus, head of caudate nucleus, insula, putamen, hippocampus, hypothalamus, amygdala, and globus pallidus while viewing the erotic video. In this regard, we assumed that human libido or the perception of sexual stimulation and the degree of physiological response to sexual stimulation were inconsistent with one another.

The premenopausal women showed significantly dominant activation in the overall brain areas compared with postmenopausal women ($P < .005$). In particular, the hypothalamus showed 4.98% activation in premenopausal women, whereas no activation was found in the postmenopausal group. It should be noted that the hypothalamus controls the endocrine system associated with sexual arousal and functioning. In addition, the higher activation ratios in the putamen (premenopausal, 12.65%; postmenopausal, 0.02%) and head of caudate nucleus (premenopausal, 23.12%; postmenopausal, 1.20%) in the premenopausal group can be attributed to sexual arousal, as demonstrated by Walter et al.[29]

Our study assessed GM volume alterations and brain functional changes in postmenopausal women and also determined the correlation between the intensities of brain activation and sex hormones. Compared with the premenopausal women, the postmenopausal women showed significantly decreased activity

Table 2. Decreased brain activity and gray matter volume in premenopausal women vs menopausal women

			MNI coordinates			
Brain areas	*t*-value	Degrees of freedom	*x*	*y*	*z*	Laterality
Decreased brain activity						
Parahippocampal gyrus	3.34	36	−32	8	−26	Lt, 90.4%
Head of caudate nucleus	2.93	36	22	21	4	Rt, 100.0%
Insula	2.78	36	48	−6	2	Rt, 84.9%
Putamen	2.77	36	22	20	1	Rt, 100.0%
Hippocampus	2.77	36	−10	−4	−19	N, 50.0%
Hypothalamus	2.68	36	−4	−2	−14	Lt, 85.2%
Amygdala	2.54	36	−30	5	−24	Lt, 100.0%
Globus pallidus	2.50	36	22	2	3	Rt, 83.3%
Decreased gray matter volume						
Insula	10.26	36	−38	4	7	Lt, 68.1%
Putamen	7.27	36	−34	−3	5	Lt, 100.0%
Parahippocampal gyrus	6.72	36	−30	9	−24	Lt, 100.0%
Amygdala	6.49	36	−31	8	−21	Lt, 75.9%
Anterior cingulate cortex	5.80	36	−1	42	19	Lt, 79.3%

Lt = left dominant hemisphere; MNI = Montreal Neurological Institute; N = non-dominant hemisphere; Rt = right dominant hemisphere.

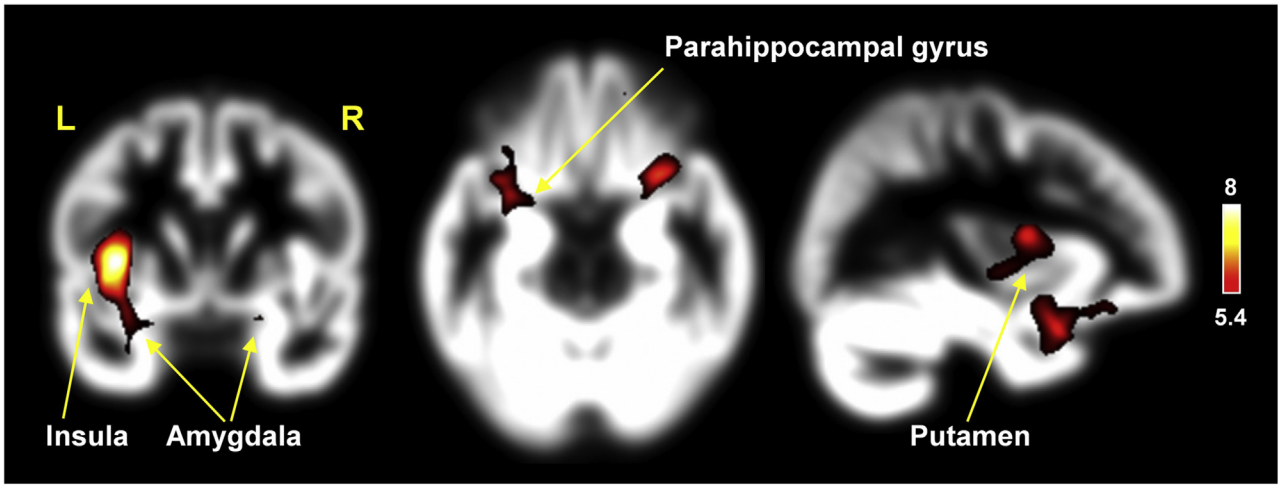

Figure 4. Decreased gray matter volumes of insula, amygdala, parahippocampal gyrus, and putamen in postmenopausal vs premenopausal women (corrected $P < .05$).

in the parahippocampal gyrus, head of caudate nucleus, insula, putamen, hippocampus, hypothalamus, amygdala, and globus pallidus while viewing the erotic video clip. Postmenopausal women exhibited decreased volumes of the insula, putamen, parahippocampal gyrus, amygdala, and anterior cingulate gyrus compared with premenopausal women. Notably, both morphometric and functional changes were observed in the insula, putamen, parahippocampal gyrus, and amygdala. Overall, our results suggest that decreased GM volume and variations in brain activity associated with insula, putamen, parahippocampal gyrus, and amygdala may be important morphometric and functional menopause-related symptoms.

Previous studies[14,30-32] have demonstrated activation of the insula in conjunction with human sexual functioning. Our current study also showed a significant difference in the activation ratios of the insula between premenopausal and postmenopausal groups (10.59% vs 0.12%, respectively), which was consistent with the studies of Ortigue et al[31] and Salonia et al[33] demonstrating the association between women's orgasm and insula activation. The activity of the insula is correlated with the

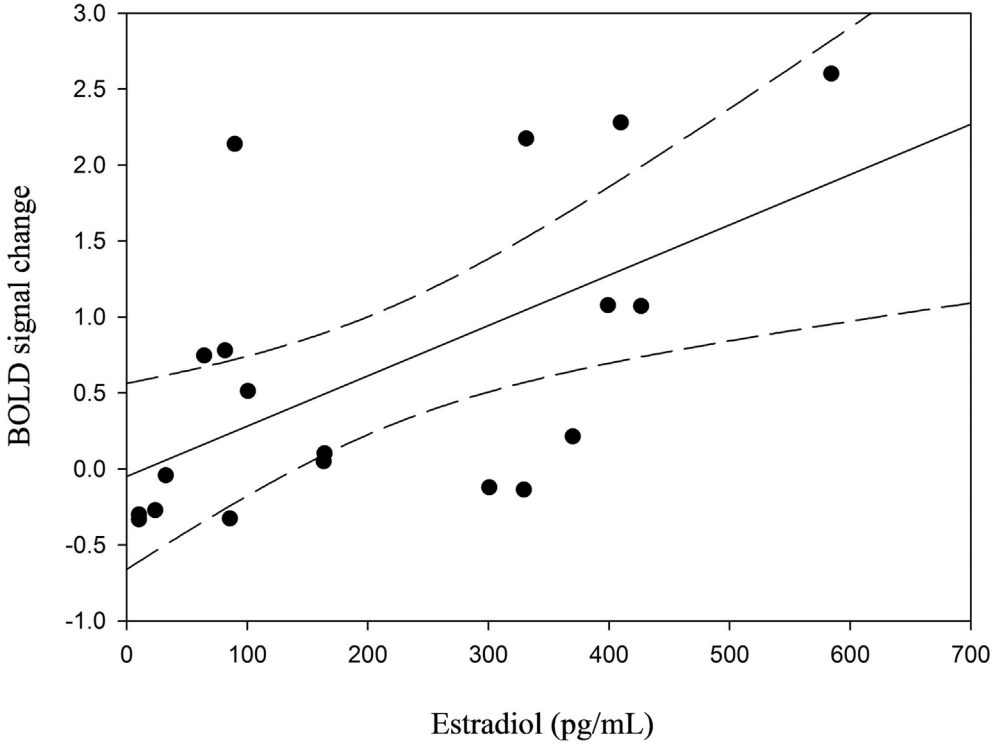

Figure 5. Correlations between the estradiol levels and changes in brain activation intensity in the insula (Pearson correlation $r = 0.588$; $P = .008$).

level of estradiol in premenopausal women ($r = 0.588$; $P = .008$). Significant activation of the amygdala was observed only in the premenopausal group. These findings may be attributed to differences in acceptance of emotional stimulation and perception response due to varying levels of emotional memory and functional adjustment of the amygdala between the 2 groups.[34,35] In addition, activation of the globus pallidus, which is one of the structures constituting the basal nuclei, can be integrated into the dorsal striatum to determine its possible association with the brain's reward system.[36]

In summary, the study revealed significant differences between the premenopausal and postmenopausal groups in GM volume and brain regions related to sexual arousal, suggesting an important link between gonadal function and the endocrine mechanism. Our study is the first to evaluate both morphometric and functional variation in connection with visual sexual arousal in postmenopausal women; however, the study has several limitations. First, large-scale deviations in individual sex hormone levels resulted in inaccurate findings in the current study. These deviations result from differences in the endocrine systems of the subjects, as well as inaccuracy of measurement methods and hormone tests not considering menstrual cycles. Second, the differences in brain activation in the 2 groups excluded the possible role of aging. Third, our study focused on menopause-related brain morphological and functional changes in postmenopausal women, without evaluating the correlation among sexual function, brain activation, and sex hormone levels; however, the relevant issue cannot be excluded in the future study. Further, other personal factors[37,38] that probably influence the morphological and functional parameters, such as emotional status, depression, marital characteristics, sexual health, cognitive functioning, religion, and personality, should be investigated in further studies.

CONCLUSION

Our study demonstrated the association between morphological changes and functional deficits during sexual arousal in postmenopausal women. It should be noted that the overlapping brain areas with functional and morphometric abnormalities are closely linked with menopausal symptoms. These findings are potentially important in understanding the brain dysfunction associated with morphological changes in menopause.

Corresponding Author: Gwang-Woo Jeong, PhD, Department of Radiology, Chonnam National University Hospital, Chonnam National University Medical School, 42 Jebong-Ro, Donggu 501-757, Republic of Korea. Tel: (82-62) 220-5881; Fax: (82-62) 226-4380; E-mail: gwjeong@jnu.ac.kr

Conflict of Interest: None.

Funding: This research was supported by the grants from National Research Foundation funded by the Korea government (Ministry of Science and Information and Communication Technology; 2018R1A2B2006260 and 2018R1C1B6005456), South Korea, and by the Chonnam National University (CNU) Research Fund for CNU distinguished research professor (2017-2022), South Korea.

STATEMENT OF AUTHORSHIP

Category 1

(a) Conception and Design
Han-Su Baek; Kwangsung Park; Gwang-Woo Jeong

(b) Acquisition of Data
Han-Su Baek; Gwang-Won Kim

(c) Analysis and Interpretation of Data
Han-Su Baek; Gwang-Won Kim; Gwang-Woo Jeong

Category 2

(a) Drafting the Article
Han-Su Baek; Gwang-Won Kim

(b) Revising It for Intellectual Content
Kwangsung Park; Gwang-Woo Jeong

Category 3

(a) Final Approval of the Completed Article
Kwangsung Park; Gwang-Woo Jeong

REFERENCES

1. Burger H. The menopausal transition—endocrinology. **J Sex Med 2008;5:2266-2273.**
2. Burger HG, Hale GE, Robertson DM, et al. A review of hormonal changes during the menopausal transition: focus on findings from the Melbourne Women's Midlife Health Project. **Hum Reprod Update 2007;13:559-565.**
3. Soules MR, Sherman S, Parrott E, et al. Executive summary: Stages of Reproductive Aging Workshop (STRAW). **Climacteric 2001;4:267-272.**
4. Kim GW, Jeong GW. Menopause-related brain activation patterns during visual sexual arousal in menopausal women: an fMRI pilot study using time-course analysis. **Neuroscience 2017;343:449-458.**
5. Lethaby A, Ayeleke RO, Roberts H. Local oestrogen for vaginal atrophy in postmenopausal women. **Cochrane Database Syst Rev 2016;8:CD001500.**
6. Avis NE, Stellato R, Crawford S, et al. Is there an association between menopause status and sexual functioning? **Menopause 2000;7:297-309.**
7. Leiblum SR, Koochaki PE, Rodenberg CA, et al. Hypoactive sexual desire disorder in postmenopausal women: US results from the Women's International Study of Health and Sexuality (WISHeS). **Menopause 2006;13:46-56.**
8. Goto M, Abe O, Miyati T, et al. 3 Tesla MRI detects accelerated hippocampal volume reduction in postmenopausal women. **J Magn Reson Imaging 2011;33:48-53.**
9. Boccardi M, Ghidoni R, Govoni S, et al. Effects of hormone therapy on brain morphology of healthy postmenopausal women: a Voxel-based morphometry study. **Menopause 2006;13:584-591.**

10. Gracia CR, Freeman EW, Sammel MD, et al. Hormones and sexuality during transition to menopause. **Obstet Gynecol 2007;109:831-840.**
11. Makara-Studzinska MT, Krys-Noszczyk KM, Jakiel G. Epidemiology of the symptoms of menopause - an intercontinental review. **Prz Menopauzalny 2014;13:203-211.**
12. Yangin HB, Sozer GA, Sengun N, et al. The relationship between depression and sexual function in menopause period. **Maturitas 2008;61:233-237.**
13. Gonzalez M, Viafara G, Caba F, et al. Sexual function, menopause and hormone replacement therapy (HRT). **Maturitas 2004;48:411-420.**
14. Jeong GW, Park K, Youn G, et al. Assessment of cerebrocortical regions associated with sexual arousal in premenopausal and menopausal women by using BOLD-based functional MRI. **J Sex Med 2005;2:645-651.**
15. Kim TH, Kang HK, Park K, et al. Localized brain metabolite changes during visual sexual stimulation in postmenopausal women: a pilot study using functional magnetic resonance spectroscopy. **Menopause 2014;21:59-66.**
16. Bartels A, Zeki S. The neural basis of romantic love. **Neuroreport 2000;11:3829-3834.**
17. Heeger DJ, Ress D. What does fMRI tell us about neuronal activity? **Nat Rev Neurosci 2002;3:142-151.**
18. Logothetis NK, Pauls J, Augath M, et al. Neurophysiological investigation of the basis of the fMRI signal. **Nature 2001;412:150-157.**
19. Kim TH, Kang HK, Jeong GW. Assessment of brain metabolites change during visual sexual stimulation in healthy women using functional MR spectroscopy. **J Sex Med 2013;10:1001-1011.**
20. Kim GW, Jeong GW. Neural mechanisms underlying sexual arousal in connection with sexual hormone levels: a comparative study of the postoperative male-to-female transsexuals and premenopausal and menopausal women. **Neuroreport 2014;25:693-700.**
21. Park K, Kang HK, Seo JJ, et al. Blood-oxygenation-level-dependent functional magnetic resonance imaging for evaluating cerebral regions of female sexual arousal response. **Urology 2001;57:1189-1194.**
22. Maravilla KR, Yang CC. Sex and the brain: the role of fMRI for assessment of sexual function and response. **Int J Impot Res 2007;19:25-29.**
23. Maravilla KR, Yang CC. Magnetic resonance imaging and the female sexual response: overview of techniques, results, and future directions. **J Sex Med 2008;5:1559-1571.**
24. Gizewski ER, Krause E, Karama S, et al. There are differences in cerebral activation between females in distinct menstrual phases during viewing of erotic stimuli: a fMRI study. **Exp Brain Res 2006;174:101-108.**
25. Freedman RR, Benton MD, Genik RJ, et al. Cortical activation during menopausal hot flashes. **Fertil Steril 2006;85:674-678.**
26. Rosen R, Brown C, Heiman J, et al. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. **J Sex Marital Ther 2000;26:191-208.**
27. Kim GW, Park K, Jeong GW. Effects of sex hormones and age on brain volume in post-menopausal women. **J Sex Med 2018;15:662-670.**
28. Song SH, Jeon H, Kim SW, et al. The prevalence and risk factors of female sexual dysfunction in young Korean women: an internet-based survey. **J Sex Med 2008;5:1694-1701.**
29. Walter M, Bermpohl F, Mouras H, et al. Distinguishing specific sexual and general emotional effects in fMRI-subcortical and cortical arousal during erotic picture viewing. **Neuroimage 2008;40:1482-1494.**
30. Yang JC, Park JI, Kim GW, et al. Effects of antidepressant treatment on sexual arousal in depressed women: a preliminary FMRI study. **Psychiatry Investig 2012;9:379-383.**
31. Ortigue S, Grafton ST, Bianchi-Demicheli F. Correlation between insula activation and self-reported quality of orgasm in women. **Neuroimage 2007;37:551-560.**
32. Komisaruk BR, Whipple B. Functional MRI of the brain during orgasm in women. **Annu Rev Sex Res 2005;16:62-86.**
33. Salonia A, Giraldi A, Chivers ML, et al. Physiology of women's sexual function: basic knowledge and new findings. **J Sex Med 2010;7:2637-2660.**
34. Costafreda SG, Brammer MJ, David AS, et al. Predictors of amygdala activation during the processing of emotional stimuli: a meta-analysis of 385 PET and fMRI studies. **Brain Res Rev 2008;58:57-70.**
35. Sergerie K, Chochol C, Armony JL. The role of the amygdala in emotional processing: a quantitative meta-analysis of functional neuroimaging studies. **Neurosci Biobehav Rev 2008;32:811-830.**
36. Rothemund Y, Preuschhof C, Bohner G, et al. Differential activation of the dorsal striatum by high-calorie visual food stimuli in obese individuals. **Neuroimage 2007;37:410-421.**
37. Kleinstäuber M. Factors associated with sexual health and well being in older adulthood. **Curr Opin Psychiatry 2017;30:358-368.**
38. Elbejjani M, Fuhrer R, Abrahamowicz M, et al. Depression, depressive symptoms, and rate of hippocampal atrophy in a longitudinal cohort of older men and women. **Psychol Med 2015;45:1931-1944.**