Published in final edited form as:

Fertil Steril. 2010 April ; 93(6): 1929–1937. doi:10.1016/j.fertnstert.2008.12.056.

Short-term Hormone Treatment Modulates Emotion Response Circuitry in Postmenopausal Women

Tiffany Love, B.S.^{†,‡}, Yolanda R. Smith, M.D., M.S.^{*}, Carol C. Persad, Ph.D.[†], Anne Tkaczyk, M.S.^{*}, and Jon-Kar Zubieta, M.D., Ph.D.^{†,‡}

[†]Department of Psychiatry, University of Michigan, Ann Arbor, U.S.A.

[‡]Molecular and Behavioral Neuroscience Institute, University of Michigan, Ann Arbor, U.S.A.

^{*}Department of Obstetrics and Gynecology, University of Michigan, Ann Arbor, U.S.A.

Abstract

Objective—To study the effects of combination hormone therapy (HT) on emotional processing in postmenopausal women using functional neuroimaging.

Design—A randomized, double-blind placebo-controlled cross-over study was performed.

Setting—A tertiary care university medical center.

Participants—Ten healthy postmenopausal women (mean age 56.9 years, S.D. = 1.4) were recruited.

Interventions—Women were randomized to the order they received combined hormone therapy, 5 ug ethinyl estradiol and 1 mg norethindrone acetate, and placebo. Volunteers received hormone therapy or placebo for 4 weeks, followed by a one month washout period, and then received the other treatment for 4 weeks. Subjects participated in an fMRI emotional processing task, where they were asked to rate emotional pictures as positive, negative, or neutral.

Main Outcome Measure—Brain activation patterns were compared between hormone therapy and placebo conditions within subjects.

Results—During negative emotional presentations, after subtracting the effect of neutral images, areas of significant differences between HT and placebo conditions were identified in the orbital, frontal, cingulate and occipital cortices. During positive emotional image presentation there were significant differences between placebo and HT conditions within the medial frontal cortex.

Conclusions—Short-term menopausal treatment with combination hormone therapy affects regional brain activity within areas implicated in emotional processing.

© 2009 American Society for Reproductive Medicine. Published by Elsevier Inc. All rights reserved.

Corresponding author and author to address reprint requests: Yolanda R. Smith, M.D., M.S., Department of Obstetrics and Gynecology, University of Michigan Health Systems, 1500 E. Medical Center Drive, Room L4224 Women's Hospital, Ann Arbor, Michigan 48109-0276. Telephone: (734) 936-7401, FAX: (734) 647-9727, ysmith@umich.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Capsule:

Using fMRI to measure neural activation patterns, combination hormone therapy modified brain activity during the processing of emotional stimuli in healthy postmenopausal women.

Keywords

Brain; women's health; neuroimaging; fMRI; emotional processing; emotional pictures; estrogen; progestin; hormones; menopause

Introduction

Menopause is a universal part of the aging process for women, involving dramatic physical and psychological changes. During this time, ovarian function declines resulting in substantial reductions in estrogen (1). This dramatic drop in estrogen is often accompanied by vasomotor symptoms, such as hot flashes and night sweats, genitourinary symptoms, and an increased risk of osteoporosis (1). Furthermore, several large longitudinal studies have demonstrated an increased risk of developing depression or depressive symptoms with the start of the menopausal transition (2–4) with the elevated risk continuing into the early postmenopausal years (4), although not all studies support this (see (5) for review).

Although there are significant health concerns to beginning hormone therapy (HT) (6), various studies confirm that HT treatments reduce vasomotor symptoms (7), the incidence of ailments such as bone fractures and colorectal cancer (6), and may impact mood and cognition (8). A growing body of evidence suggests combined or unopposed estrogen therapy can alter mood functioning in menopausal women, possibly through its effects on the central nervous system (CNS) [see review in (9)]. Overall, the literature is most compelling for a positive effect of estrogen on mood in women undergoing the menopausal transition and is more controversial for use in postmenopausal mood issues (10–12). However, many studies have not controlled for potential confounding factors such as vasomotor symptoms and sleep quality. Some studies have shown that following HT, healthy non-depressed postmenopausal women have fewer depressive symptoms (8,13), while others suggest that the addition of a progestin may diminish estrogen's positive effect on mood (14).

Despite the evidence supporting HT's role in modifying mood in menopausal women, the precise alterations in neural activity underlying these changes are not fully understood. It is well known that estrogen receptors are located throughout the brain, most notably within the limbic system, which plays a critical role in emotion processing (15). Estrogen plays a neuromodulatory role in the CNS, exerting its effects on the brain by adjusting both the concentration and activity of various neurotransmitters and their receptors as well as altering other cellular events, such as gene transcription (see (16–19)). However, mechanistic studies describing how HT modulates functional brain activity associated with emotional processing in humans are largely absent.

Through the use of functional magnetic resonance imaging (fMRI), a non-invasive neuroimaging technique, it is possible to examine changes in brain activity during the processing of emotional stimuli and to determine how HT alters this activity. Although several studies have assessed the effects of HT on functional activity associated with cognitive tasks in postmenopausal women (20–24) no study to date has examined such effects on an emotional processing task. Here, we report the effect of dual administration of estrogen and progestin on functional activity during an emotional processing task in a placebo-controlled fMRI study of postmenopausal women. We hypothesized that in comparison to the placebo condition, HT would differentially recruit limbic brain regions known to be involved in emotion. This work is part of a comprehensive evaluation of hormone effects on brain activity for which the cognitive processing results have been previously reported (23,25).

Methods

Subjects

As part of an extensive assessment of hormone effects on neural processing, a group of 10 healthy postmenopausal women, 56 – 60 years of age (mean age 56.9 years, S.D. = 1.4), were recruited by advertisement. Menopause was defined as the absence of menstrual periods for 1 year for those with intact reproductive organs or the time of hysterectomy with bilateral salpingo-oophorectomy. After an initial phone screening, the women had personal interviews in which medical and psychiatric histories, screening laboratory tests (fasting cholesterol, glucose, estradiol, complete blood count, TSH, electrolytes and liver function tests), and a physical exam including pelvic examination and pelvic ultrasound were obtained. All women had normal pap smears and mammograms within one year prior to participation in the study.

Women were free of significant general medical, neurological or psychiatric illness; had not received hormone therapy in the last 3 months; had never experienced a head injury with loss of consciousness; and had no history of drug or alcohol abuse or dependence. All participants were right handed, were nonsmokers, and were taking no medications with actions in the central nervous system. Exclusion criteria included an endometrial lining greater than 5 mm, ovarian pathology on ultrasound, migraines, liver dysfunction, history of thromboembolic disease, uncontrolled thyroid disease, fasting cholesterol > 300 mg/dl, fasting triglycerides > 300 mg/dl, and fasting glucose >140 mg/dl. After a full description of the study, written informed consent was obtained. All procedures were approved by the University of Michigan Institutional Review Board.

Study Design

The study design utilized a randomized, double blind, placebo-controlled crossover design of hormone therapy versus placebo. We chose an available FDA approved combination HT product. Subjects were randomized to the order they received hormone therapy with 5 ug ethinyl estradiol and 1 mg norethindrone acetate (Femhrt, Warner Chilcott, PLC, United Kingdom; provided by Pfizer Pharmaceuticals, New York City, New York). Randomization was performed with a computer generated random number list. Prior to beginning treatment the subjects had baseline neuropsychological testing. Subjects received hormone therapy or placebo for 4 weeks, followed by a one month washout period with no medications, and then received the other treatment for 4 weeks. At the end of each 4 week treatment period an fMRI study was performed. Pill counts were done after each treatment period to document compliance.

Neuropsychological testing to exclude the presence of dementia and depression included the following measures: 1) Mini-Mental State Examination (26) as a brief screening measure of dementia and 2) Geriatric Depression Rating Scale (27) to exclude the presence of depression. No vasomotor or sleep measures were included in this study.

Emotional Processing Task

The pictures were chosen from the International Affective Picture System (IAPS) (28,29) and presented to subjects through a set of RF-shielded goggles mounted to the headcoil (Resonance Technology Inc., Northridge, CA). Pictures were chosen with affective content rated as positive, negative or neutral by a normative female sample. Examples of positive images included pictures of puppies, sunsets, and babies; whereas negative images included pictures of guns, crying people, and cemeteries. Neutral pictures included light switches, abstract art, and buildings. Two equated sets of picture stimuli were developed and presentation of the sets was counterbalanced for each subject across the placebo and treatment conditions. In the

scanner, the pictures were presented in a blocked design across 4 runs. Each run had a duration of approximately 4–5 minutes with a 30 second break between runs.

In each session, blocks of 4 pictures of each affective state were counterbalanced for a total of 48 pictures per run. Each picture was presented for 3.5 seconds with a 1.5 second interstimulus interval. A commercial software package (E-Prime, Psychology Software Tools Inc, Pittsburg, PA) running on a computer in the MRI control room controlled the timing of the stimulus presentation. The total number of scans was 144 with an interscan interval of 2 seconds. Participants were asked to rate each picture as positive, negative or neutral by pressing one of three buttons on a MRI-compatible response pad. Accuracy and response time was recorded. The overall task was preceded by the presentation of detailed instructions during which no data was acquired. To minimize performance differences between subjects, prior to fMRI data collection, participants practiced the task on a computer outside the scanner until comfortable with the task.

FMRI Acquisition and Processing

All scans were acquired using a 3T whole body MRI scanner (General Electric, Milwaukee, WI) equipped with a standard headcoil. Anatomical MRI scans were acquired axially in all subjects with an SPGR 3D volumetric acquisition (TR 9.6 / TE 3.3 / IR PREP 200ms / flip angle 17 degrees / bandwidth 15.63 / 24cm F.O.V. / 1.5mm slice thickness / 106–110 slices / 256×256 matrix / 2 nex) for anatomical localization and coregistration to standardized stereotactic coordinates. FMRI acquisition was sensitized for the blood oxygen level-dependent (BOLD) effect using a T2* weighted single-shot spiral pulse sequence (30) with 32 oblique-axial slices prescribed to be approximately parallel to the AC-PC line (Spiral GRE, TE = 25, TR = 2000, FA = 60°, 4 mm-thick contiguous slices, 24 cm FOV, image matrix = 64 dia). Image reconstruction included processing steps to remove distortions caused by magnetic field inhomogeneity and other sources of misalignment to the structural data (31). Data were sinc-interpolated in time, slice-by-slice, to correct for the staggered sequence of slice acquisition (32).

The first four functional volumes of each run were discarded to remove magnetic saturation effects. The remaining functional images were realigned to the first volume to eliminate movement artifacts using SPM2-based algorithms (33). Realignment parameters for each subject were carefully examined to ensure subject's head movement did not exceed 2 mm. In addition, these parameters were included in the analyses as confounds. Subject's MRI and functional images were coregistered to each other and then spatially normalized into standard stereotactic space (International Conference on Brain Mapping (ICBM) stereotactic space) via non-linear warping using image processing tools within SPM2 (33). Finally, a three-dimensional Gaussian smoothing kernel set at 8 mm full-width-half-maximum (FWHM) was applied to each subject's functional data to accommodate for residual anatomical variability and to improve signal to noise ratios.

FMRI Data Analyses

All fMRI data analyses were conducted using the general linear model in SPM2 (Wellcome Department of Cognitive Neurology, London, UK). For the first level analyses, for both placebo and HT conditions, contrast images were generated for each subject to assess differences in activation between viewing pictures with affective content and viewing of pictures with neutral content. For main effects, voxels were identified as significant only when passing a statistical threshold of $p \leq 0.05$ corrected for multiple comparisons at the cluster-level.

To evaluate the effect of hormone therapy, the contrast images were placed into ICBM stereotactic space using the transformation matrix derived from the linear and non-linear warping transformation matrices (described above). Then, the contrast images for each subject during hormone therapy and placebo conditions were analyzed at the group-level using both paired and one-sample t-tests. Numerical differences between groups were determined by averaging the values of voxels contained in an area of significant differences, down to a threshold of $T = 3$. These data were then plotted and examined for regional differences between conditions to eliminate the possibility that significant effects in the voxel-by-voxel comparisons were caused by artifactual data or outliers. Effects of treatment were identified using a statistical threshold of $p \leq 0.001$, uncorrected for multiple comparisons, to identify significant voxels for all comparisons.

Results

The average age of the participants in this study was 56.9 years. All 10 subjects completed the study protocol and pill counts documented completion of the medication. The demographic and baseline information is described in Table 1. The baseline neuropsychological testing demonstrated that these volunteers were without evidence of dementia or depression. During performance of the task, postmenopausal women identified negative images correctly in $88 \pm 7\%$ of cases during placebo and in $88 \pm 11\%$ of cases during HT administration. Correct identification was obtained for positive images in $88 \pm 9\%$ of cases during placebo and in $87 \pm 10\%$ during HT administration and for neutral images $63 \pm 17\%$ of cases during placebo and $60 \pm 17\%$ during HT administration. A two-way analysis of variance yielded a main effect for stimulus type ($F(2,59)=30.06$, $p<0.01$), however no main effect of HT was observed ($F(1,59)=0.19$, $p=0.66$). The interaction effect was also non-significant ($F(2,59)=0.08$, $p=0.93$).

Areas of activation during negative emotional image presentation

Areas of significant activation during viewing of negative pictures after subtracting the effect of neutral images (negative minus neutral, first level analysis), were obtained in large areas within the occipital cortex (left and right), posterior cingulate extending into the precuneus, and right hippocampus extending into the amygdala and surrounding cortex (Table 2; Figure 1a). In addition, one area, the left superior parietal cortex, showed significant deactivation during the presentation of negative pictures relative to neutral pictures (neutral minus negative, first level analysis; Table 2; Figure 1b).

Areas of activation during positive emotional image presentation

During positive emotional image presentation, after subtracting the effect of neutral images (positive minus neutral, first level analysis), there was significant activation in the medial prefrontal cortex and posterior cingulate (Table 2; Figure 1c).

Hormone effects on activation during negative emotional image presentation

Significant differences between HT and placebo conditions were obtained in the orbitofrontal cortex bilaterally, left occipital cortex, the right precentral gyrus and posterior cingulate. The HT condition was associated with a more pronounced activation of these regions (Table 3; Figure 2a).

Areas of significantly greater activation were detected during placebo compared to the HT condition within the dorsolateral prefrontal cortex, postcentral gyrus, and dorsal anterior cingulate (Table 3; Figure 2b).

Hormone effects on activation during positive emotional image presentation

Significant differences in activation were detected within the left medial frontal cortex where the placebo condition was associated with greater activation relative to the HT condition (Table 3; Figure 2c).

Discussion

The present study demonstrated the modulation of blood oxygen level-dependent (BOLD) signal responses to emotional stimuli by combined estrogen/progestin hormone therapy in postmenopausal women. The BOLD signal indicates neural activity in areas of the brain, as hemoglobin oxygenation changes. In response to negative pictures, greater BOLD activation during HT treatment relative to placebo was noted within the occipital cortex, posterior cingulate, orbitofrontal cortex, and precentral gyrus, while lesser BOLD activation was noted in the dorsolateral prefrontal cortex, postcentral gyrus and dorsal anterior cingulate. In response to positive pictures a reduction in BOLD activation during HT treatment relative to placebo was noted in the medial frontal cortex.

Increases in activity within the occipital cortex have been demonstrated previously during visual emotional processing tasks (34–36) and the results of our study suggest that this effect is enhanced with hormone treatment. Although visual association cortices are normally mobilized during the processing of visual stimuli, some investigators have speculated that important input, like affective stimuli, may prompt enhanced processing with these regions as part of an emotional processing circuit originating in attention centers such as the anterior cingulate (37) or within limbic areas like the amygdala (38). Investigators have pointed to the evolutionary advantage in recognizing motivationally significant stimuli (35,39) as an explanation for this phenomenon. The increased activity seen with hormone treatment suggests enhanced responsiveness to emotional visual stimuli within this region relative to placebo treatment. While this finding may be compatible with previous reports describing increased arousal in response to salient negative material following hormone therapy (40), further investigation will be necessary to determine the source of the differences observed here.

BOLD activations in response to negative stimuli were noted in the posterior cingulate. This finding is consistent with prior research showing this region to be activated by emotionally significant stimuli, such as emotionally salient words (41,42), distressing imagery (43), and angry faces (44), when compared to neutral stimuli. Specifically, the posterior cingulate is believed to be involved in the evaluation of the importance of sensory events and in the interaction between emotion and memory (41,45). Enhanced activity following hormone therapy was noted in this area, perhaps indicating increased evaluative emotional processing of the stimuli following hormone treatment.

The orbitofrontal cortex exhibited significantly enhanced BOLD activation in the HT condition relative to the placebo condition during the viewing of negative pictures. The orbitofrontal cortex, frequently described for the role it plays in decision-making processes, has also been noted for its involvement in emotion (see review (46)). Indeed, some researchers hypothesize this region may be recruited during the processing of emotional material as patients with orbitofrontal damage have been shown to be defective in their ability to process and experience the affective qualities of emotional stimuli (46,47). Evidence obtained in normal controls demonstrated increases in activity following arousing, particularly aversive/unpleasant, stimuli (48,49). Also, the activity within this region has been demonstrated to be modulated by both valence and arousal (50). It is possible that the increased activity we see within this region during the HT condition may reflect higher levels of arousal to negative material (40), however, as subjective arousal to the stimuli was not recorded, this is an area that should be followed up on.

Conversely, we note reduced BOLD responses within the dorsolateral prefrontal cortex and dorsal anterior cingulate for the HT condition relative to the placebo condition in the negative emotion task. These regions, like the orbitofrontal cortex, are well known for the roles they play in cognition; however, each have also been implicated in emotional processing (51,52). The dorsolateral prefrontal cortex is specifically posited to play a role in the suppression of emotion (51). The anterior cingulate has been hypothesized to regulate emotional experiences, particularly the perception of emotional stimuli (52). Indeed, activity within the anterior cingulate has been shown to be inversely related to the intensity of negative affect experienced following the presentation of pictures (51). Older adults have been shown to experience less negative affect with age (53,54) and show diminished physiological responses to emotional stimuli (55). The differences emerging between HT and placebo conditions may reflect a return of emotional responsivity in these older women following hormone treatment; however, additional study is warranted.

A single region, the left medial frontal cortex, showed greater BOLD activation in response to positive stimuli in the placebo condition relative to the HT condition. Activity within the left medial frontal cortex has been previously found to be associated with the induction of both positive and negative emotional states (56–58). Older women, compared to their younger counterparts, experience less negative affect (53,54) and in the absence of HT may find positive images more arousing relative to negative, whereas women on HT show the opposite pattern (i.e. higher arousal to negative pictures) (40). This may give details as to the reduced brain activity in this region following hormone treatment, however, this source of this difference needs to be assessed in a future study.

In addition to the regions discussed above, HT also appeared to affect activity within the right precentral and postcentral gyri with negative stimuli. These areas are primarily noted for their motor and somatosensory functions; however, their role in emotional processing has yet to be fully ascertained.

In summary, this study adds to the body of evidence suggesting that HT can modify emotional processing in postmenopausal women. Our study suggests that combination HT acts to modify brain activity associated with the evaluation and categorization of emotional stimuli. Ascertaining the effects of short-term HT on emotional processes is of particular importance given the current controversy over the potential benefits and risks of hormone therapy. While this pilot study is strengthened by its randomized and intra-subject design, it is limited by its small sample size and lack of additional behavioral. In addition, physiological measures to examine hot flashes and sleep disturbances were not included and improvement of these menopausal symptoms with HT may have influenced the study findings. We recognize that the use of an ethinyl estradiol and norethindrone acetate combination HT product raises the possibility that the brain regions activated may not be identical to those that might be identified with estradiol and progesterone. However, in our study HT did activate brain regions hypothesized to be influenced by estrogen. Further studies involving women earlier in menopause, separating estrogen and progesterone effects, and with longer treatment duration should be conducted to fully examine the effects of hormone therapies on emotional processing.

Acknowledgments

We thank the fMRI staff (Eve Gochis, Luis Hernandez, Ph.D., Keith Newnham, and Douglas Noll, Ph.D.) at the University of Michigan, Ann Arbor for their assistance in this study.

Supported in part by Grant K23RR017043 from the National Center for Research Resources and an investigator initiated grant from Pfizer Pharmaceuticals Group.

References

1. WHO. Research on the menopause in the 1990s. Report of a WHO Scientific Group; World Health Organ Tech Rep Ser. 1996. p. 1-107.
2. Freeman EW, Sammel MD, Lin H, Nelson DB. Associations of hormones and menopausal status with depressed mood in women with no history of depression. *Arch Gen Psychiatry* 2006;63:375–382. [PubMed: 16585466]
3. Cohen LS, Soares CN, Vitonis AF, Otto MW, Harlow BL. Risk for new onset of depression during the menopausal transition: the Harvard study of moods and cycles. *Arch Gen Psychiatry* 2006;63:385–390. [PubMed: 16585467]
4. Bromberger JT, Matthews KA, Schott LL, Brockwell S, Avis NE, Kravitz HM, et al. Depressive symptoms during the menopausal transition: the Study of Women's Health Across the Nation (SWAN). *J Affect Disord* 2007;103:267–272. [PubMed: 17331589]
5. Vesco KK, Haney EM, Humphrey L, Fu R, Nelson HD. Influence of menopause on mood: a systematic review of cohort studies. *Climacteric : the journal of the International Menopause Society* 2007;10:448–465. [PubMed: 18049938]
6. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *Jama* 2002;288:321–333. [PubMed: 12117397]
7. MacLennan A, Lester S, Moore V. Oral estrogen replacement therapy versus placebo for hot flushes: a systematic review. *Climacteric* 2001;4:58–74. [PubMed: 11379379]
8. Miller KJ, Conney JC, Rasgon NL, Fairbanks LA, Small GW. Mood symptoms and cognitive performance in women estrogen users and nonusers and men. *J Am Geriatr Soc* 2002;50:1826–1830. [PubMed: 12410901]
9. Soares CN, Poitras JR, Prouty J. Effect of reproductive hormones and selective estrogen receptor modulators on mood during menopause. *Drugs Aging* 2003;20:85–100. [PubMed: 12534310]
10. Cohen LS, Soares CN, Poitras JR, Prouty J, Alexander AB, Shifren JL. Short-term use of estradiol for depression in perimenopausal and postmenopausal women: a preliminary report. *The American journal of psychiatry* 2003;160:1519–1522. [PubMed: 12900318]
11. Resnick SM, Maki PM, Rapp SR, Espeland MA, Brunner R, Coker LH, et al. Effects of combination estrogen plus progestin hormone treatment on cognition and affect. *J Clin Endocrinol Metab* 2006;91:1802–1810. [PubMed: 16522699]
12. Morrison MF, Kallan MJ, Ten Have T, Katz I, Tweedy K, Battistini M. Lack of efficacy of estradiol for depression in postmenopausal women: a randomized, controlled trial. *Biological psychiatry* 2004;55:406–412. [PubMed: 14960294]
13. Hlatky MA, Boothroyd D, Vittinghoff E, Sharp P, Whooley MA. Quality-of-life and depressive symptoms in postmenopausal women after receiving hormone therapy: results from the Heart and Estrogen/Progestin Replacement Study (HERS) trial. *Jama* 2002;287:591–597. [PubMed: 11829697]
14. Zweifel JE, O'Brien WH. A meta-analysis of the effect of hormone replacement therapy upon depressed mood. *Psychoneuroendocrinology* 1997;22:189–212. [PubMed: 9203229]
15. McEwen BS, Alves SE, Bulloch K, Weiland NG. Ovarian steroids and the brain: implications for cognition and aging. *Neurology* 1997;48:S8–S15. [PubMed: 9153161]
16. McEwen B. Estrogen actions throughout the brain. *Recent Prog Horm Res* 2002;57:357–384. [PubMed: 12017552]
17. Moses EL, Drevets WC, Smith G, Mathis CA, Kalro BN, Butters MA, et al. Effects of estradiol and progesterone administration on human serotonin 2A receptor binding: a PET study. *Biol Psychiatry* 2000;48:854–860. [PubMed: 11063980]
18. Moses-Kolko EL, Berga SL, Greer PJ, Smith G, Cidis Meltzer C, Drevets WC. Widespread increases of cortical serotonin type 2A receptor availability after hormone therapy in euthymic postmenopausal women. *Fertil Steril* 2003;80:554–559. [PubMed: 12969697]
19. Kugaya A, Epperson CN, Zoghbi S, van Dyck CH, Hou Y, Fujita M, et al. Increase in prefrontal cortex serotonin 2A receptors following estrogen treatment in postmenopausal women. *Am J Psychiatry* 2003;160:1522–1524. [PubMed: 12900319]

20. Resnick SM, Maki PM, Golski S, Kraut MA, Zonderman AB. Effects of estrogen replacement therapy on PET cerebral blood flow and neuropsychological performance. *Horm Behav* 1998;34:171–182. [PubMed: 9799627]
21. Shaywitz SE, Shaywitz BA, Pugh KR, Fulbright RK, Skudlarski P, Mennel WE, et al. Effect of estrogen on brain activation patterns in postmenopausal women during working memory tasks. *Jama* 1999;281:1197–1202. [PubMed: 10199429]
22. Stevens MC, Clark VP, Prestwood KM. Low-dose estradiol alters brain activity. *Psychiatry Res* 2005;139:199–217. [PubMed: 16084069]
23. Smith YR, Love T, Persad CC, Tkaczyk A, Nichols TE, Zubieta JK. Impact of combined estradiol and norethindrone therapy on visuospatial working memory assessed by functional magnetic resonance imaging. *J Clin Endocrinol Metab* 2006;91:4476–4481. [PubMed: 16912129]
24. Eberling JL, Reed BR, Coleman JE, Jagust WJ. Effect of estrogen on cerebral glucose metabolism in postmenopausal women. *Neurology* 2000;55:875–877. [PubMed: 10994014]
25. Persad CC, Zubieta JK, Love T, Wang H, Tkaczyk A, Smith YR. Enhanced Neuroactivation during Verbal Memory Processing in Postmenopausal Women Receiving Short Term Hormone Therapy. *Fertility and Sterility*. in press.
26. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189–198. [PubMed: 1202204]
27. Yesavage JA, Adey M, Werner PD. Development of a geriatric behavioral self-assessment scale. *J Am Geriatr Soc* 1981;29:285–288. [PubMed: 7195410]
28. Lang, PJ.; Greenwald, MK. The international affective picture system standardization procedure and initial group results for affective judgments. In: Gainesville, FL., editor. Center for Research in Psychophysiology. University of Florida; 1988.
29. Lang PJ, Greenwald MK, Bradley MM, Hamm AO. Looking at pictures: affective, facial, visceral, and behavioral reactions. *Psychophysiology* 1993;30:261–273. [PubMed: 8497555]
30. Noll DC, Cohen JD, Meyer CH, Schneider W. Spiral K-space MR imaging of cortical activation. *Journal of magnetic resonance imaging : JMRI* 1995;5:49–56. [PubMed: 7696809]
31. Noll, DC.; Stenger, VA.; Vazquez, AL.; Peltier, SJ. Spiral Scanning in Functional MRI. In: Ctw, M.; Pa, B., editors. *Medical Radiology: Functional MRI*. Heidelberg: Springer-Verlag; 1999. p. 149-169.
32. Acquire, GK.; D'Esposito, M. Experimental Design for Brain fMRI. In: Ctw, M.; Pa, B., editors. *Medical Radiology: Functional MRI*. Heidelberg: Springer-Verlag; 1999. p. 369-380.
33. Friston KJ, Ashburner J, Frith CD, Poline JB, Heather JD, Frackowiak RSJ. Spatial registration and normalization of images. *Human Brain Mapping* 1995;3:165–189.
34. Reiman EM, Lane RD, Ahern GL, Schwartz GE, Davidson RJ, Friston KJ, et al. Neuroanatomical correlates of externally and internally generated human emotion. *Am J Psychiatry* 1997;154:918–925. [PubMed: 9210741]
35. Lang PJ, Bradley MM, Fitzsimmons JR, Cuthbert BN, Scott JD, Moulder B, et al. Emotional arousal and activation of the visual cortex: an fMRI analysis. *Psychophysiology* 1998;35:199–210. [PubMed: 9529946]
36. Lane RD, Fink GR, Chau PM, Dolan RJ. Neural activation during selective attention to subjective emotional responses. *Neuroreport* 1997;8:3969–3972. [PubMed: 9462476]
37. Ueda K, Okamoto Y, Okada G, Yamashita H, Hori T, Yamawaki S. Brain activity during expectancy of emotional stimuli: an fMRI study. *Neuroreport* 2003;14:51–55. [PubMed: 12544830]
38. Morris JS, Friston KJ, Buchel C, Frith CD, Young AW, Calder AJ, et al. A neuromodulatory role for the human amygdala in processing emotional facial expressions. *Brain* 1998;121(Pt 1):47–57. [PubMed: 9549487]
39. Cacioppo JT, Gardner WL. Emotion. *Annu Rev Psychol* 1999;50:191–214. [PubMed: 10074678]
40. Pruis TA, Neiss MB, Leigland LA, Janowsky JS. Estrogen modifies arousal but not memory for emotional events in older women. *Neurobiol Aging*. 2007
41. Maddock RJ, Garrett AS, Buonocore MH. Posterior cingulate cortex activation by emotional words: fMRI evidence from a valence decision task. *Hum Brain Mapp* 2003;18:30–41. [PubMed: 12454910]
42. Maddock RJ, Buonocore MH. Activation of left posterior cingulate gyrus by the auditory presentation of threat-related words: an fMRI study. *Psychiatry Res* 1997;75:1–14. [PubMed: 9287369]

43. Sinha R, Lacadie C, Skudlarski P, Wexler BE. Neural circuits underlying emotional distress in humans. *Ann N Y Acad Sci* 2004;1032:254–257. [PubMed: 15677422]
44. Sprengelmeyer R, Rausch M, Eysel UT, Przuntek H. Neural structures associated with recognition of facial expressions of basic emotions. *Proc Biol Sci* 1998;265:1927–1931. [PubMed: 9821359]
45. Maddock RJ, Garrett AS, Buonocore MH. Remembering familiar people: the posterior cingulate cortex and autobiographical memory retrieval. *Neuroscience* 2001;104:667–676. [PubMed: 11440800]
46. Bechara A, Damasio H, Damasio AR. Emotion, decision making and the orbitofrontal cortex. *Cereb Cortex* 2000;10:295–307. [PubMed: 10731224]
47. Angrilli A, Palomba D, Cantagallo A, Maietti A, Stegagno L. Emotional impairment after right orbitofrontal lesion in a patient without cognitive deficits. *Neuroreport* 1999;10:1741–1746. [PubMed: 10501567]
48. Frey S, Kostopoulos P, Petrides M. Orbitofrontal involvement in the processing of unpleasant auditory information. *Eur J Neurosci* 2000;12:3709–3712. [PubMed: 11029640]
49. Perlstein WM, Elbert T, Stenger VA. Dissociation in human prefrontal cortex of affective influences on working memory-related activity. *Proc Natl Acad Sci U S A* 2002;99:1736–1741. [PubMed: 11818573]
50. Lewis PA, Critchley HD, Rotshtein P, Dolan RJ. Neural correlates of processing valence and arousal in affective words. *Cereb Cortex* 2007;17:742–748. [PubMed: 16699082]
51. Phan KL, Fitzgerald DA, Nathan PJ, Moore GJ, Uhdé TW, Tancer ME. Neural substrates for voluntary suppression of negative affect: a functional magnetic resonance imaging study. *Biol Psychiatry* 2005;57:210–219. [PubMed: 15691521]
52. Phillips ML, Drevets WC, Rauch SL, Lane R. Neurobiology of emotion perception I: The neural basis of normal emotion perception. *Biol Psychiatry* 2003;54:504–514. [PubMed: 12946879]
53. Carstensen LL, Charles ST. Emotion in the Second Half of Life. *Current Directions in Psychological Science* 1998;7:144–149.
54. Charles ST, Reynolds CA, Gatz M. Age-related differences and change in positive and negative affect over 23 years. *J Pers Soc Psychol* 2001;80:136–151. [PubMed: 11195886]
55. Smith DP, Hillman CH, Duley AR. Influences of age on emotional reactivity during picture processing. *J Gerontol B Psychol Sci Soc Sci* 2005;60:P49–P56. [PubMed: 15643039]
56. Lane RD, Reiman EM, Ahern GL, Schwartz GE, Davidson RJ. Neuroanatomical correlates of happiness, sadness, and disgust. *Am J Psychiatry* 1997;154:926–933. [PubMed: 9210742]
57. Lane RD, Reiman EM, Bradley MM, Lang PJ, Ahern GL, Davidson RJ, et al. Neuroanatomical correlates of pleasant and unpleasant emotion. *Neuropsychologia* 1997;35:1437–1444. [PubMed: 9352521]
58. Teasdale JD, Howard RJ, Cox SG, Ha Y, Brammer MJ, Williams SC, et al. Functional MRI study of the cognitive generation of affect. *Am J Psychiatry* 1999;156:209–215. [PubMed: 9989556]

Figure 1. Regional brain activity during the emotional image presentation

Images display areas where significant differences in BOLD activation were detected for the contrasts negative > neutral (A), neutral > negative (B), and positive > neutral (C). No significant differences were noted for the neutral > positive comparison. Images are displayed in neurological convention (right of the image is the right side of the brain). T scores are represented by the pseudocolor scale given at the lower right corner of the image and are superimposed over anatomical MRI images. Threshold for display of results was set at $T = 3$. All regions were significant at $p < 0.05$ following correction for multiple comparisons. MPFC = Medial Prefrontal Cortex, SPC = Superior Parietal Cortex, PCING = Posterior Cingulate, OCC = Occipital Cortex, HIPP = hippocampus.

Figure 2. Effects of HT on emotional image presentation

Images display areas where (A) greater BOLD activity was detected in the HT condition relative to the placebo condition during negative image presentation (negative – neutral) and (B) lesser BOLD activity was detected in the HT condition relative to the placebo condition during negative image presentation (negative – neutral) or (C) during positive image presentation. DLPFC = Dorsolateral Prefrontal Cortex, MFC = Medial Frontal Cortex, PCG = Precentral Gyrus, POG = Postcentral Gyrus, DACING = Dorsal Anterior Cingulate, PCING = Posterior Cingulate, OCC = Occipital Cortex.

Table 1

Demographic Data

	<u>Mean (Standard Deviation)</u>
Age	56.9 (1.4)
Education	16.3 (1.9)
Mini Mental State Exam (MMSE)	28.6 (1.9)
Geriatric Depression Scale	0.4 (1.0)
Age of Menopause	50.0 (2.7)
Years Post Menopause	6.9 (2.8)
Body Mass Index	25.5 (4.0)

Table 2

Effect of Task, Emotional Image Presentation

► <i>Negative Images</i>			
Region [*]	Coordinates (x, y, z) [†]	Z	Cluster Size [‡]
Negative > Neutral			
Right Occipital Cortex (multiple peaks)	52, -68, -4	5.70	31432
	14, -84, 38	4.12	3216
Left Occipital Cortex	-54, -68, -2	5.54	19224
Posterior Cingulate (extending into the Precuneus)	0, -52, 46	4.28	20016
Right Hippocampus (extending into the amygdala/surrounding cortex)	22, -12, -14	4.13	7552
Neutral > Negative			
Left Superior Parietal Cortex	-42, -26, 54	4.91	13024
► <i>Positive Images</i>			
Region [*]	Coordinates (x, y, z) [†]	Z	Cluster Size [‡]
Positive > Neutral			
Medial Prefrontal Cortex	-2, 44, -6	4.61	7456
Posterior Cingulate (extending into the Precuneus)	2, -60, 22	4.30	24920

[†]Coordinates (x,y,z) refer to the ICBM coordinates where the significant differences were centered in mm.

[‡]Cluster size is expressed in voxels of 1³ mm.

* All regions significant at $p \leq 0.05$, corrected for multiple comparisons.

Table 3

Effect of Hormone Therapy on Activity During Emotional Image Presentation

► <i>Negative Images</i>			
Region [*]	Coordinates (x, y, z) [†]	Z	Cluster Size [‡]
Hormones > Placebo			
Right Orbitofrontal Cortex	16, 52, -10	3.11	1280
Left Orbitofrontal Cortex	-8, 52, -16	3.57	368
Right Precentral Gyrus	14, -30, 76	3.35	928
Posterior Cingulate	-6, -48, 12	4.03	1104
Left Occipital Cortex	-32, -84, 18	3.75	544
Placebo > Hormones			
Left Dorsolateral Prefrontal Cortex	-38, 6, 30	3.32	960
Right Postcentral Gyrus	60, -14, 34	3.63	1400
Dorsal Anterior Cingulate	12, 32, 28	3.47	1032
► <i>Positive Images</i>			
Region [*]	Coordinates (x, y, z) [†]	Z	Cluster Size [‡]
Placebo > Hormones			
Left Medial Frontal Cortex	-12, 14, 56	3.44	224

[†] Coordinates (x,y,z) refer to the ICBM coordinates where the significant differences were centered in mm.

[‡] Cluster size is expressed in voxels of 1³ mm.

^{*} All regions significant at $p \leq 0.001$, uncorrected for multiple comparisons.