Short-term hormone treatment modulates emotion response circuitry in postmenopausal women

Tiffany Love, B.S.,[a,b] *Yolanda R. Smith, M.D., M.S.,*[c] *Carol C. Persad, Ph.D.,*[a] *Anne Tkaczyk, M.S.,*[c] *and Jon-Kar Zubieta, M.D., Ph.D.*[a,b]

[a] Department of Psychiatry, [b] Molecular and Behavioral Neuroscience Institute, and [c] Department of Obstetrics and Gynecology, University of Michigan, Ann Arbor, Michigan

Objective: To study the effects of combination hormone therapy (HT) on emotional processing in postmenopausal women with use of functional neuroimaging.
Design: A randomized, double-blind, placebo-controlled crossover study was performed.
Setting: A tertiary care university medical center.
Participant(s): Ten healthy postmenopausal women (mean age 56.9 years, SD = 1.4 years) were recruited.
Intervention(s): Women were assigned randomly to the order they received combined HT, 5 μg ethinyl E_2 and 1 mg norethindrone acetate, and placebo. Volunteers received HT or placebo for 4 weeks, followed by a 1-month washout period, and then received the other treatment for 4 weeks. Subjects participated in a functional magnetic resonance imaging emotional processing task, where they were asked to rate emotional pictures as positive, negative, or neutral.
Main Outcome Measure(s): Brain activation patterns were compared between HT and placebo conditions within subjects.
Result(s): 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 HT affects regional brain activity within areas implicated in emotional processing. (Fertil Steril® 2010;93:1929–37. ©2010 by American Society for Reproductive Medicine.)

Key Words: Brain, women's health, neuroimaging, fMRI, emotional processing, emotional pictures, estrogen, progestin, hormones, menopause

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 levels (1). This dramatic drop in estrogen level 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 development of 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 Vesco et al. [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) and 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 that combined or unopposed estrogen therapy can alter mood functioning in menopausal women, possibly through its effects on the central nervous system (see review in Soares et al. [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 after HT, healthy nondepressed postmenopausal women have fewer depressive

Received July 29, 2008; revised November 6, 2008; accepted December 10, 2008; published online February 24, 2009.
T.L. has nothing to disclose. The husband of Y.R.S. participates on lecture bureaus for Eli Lilly Co., and Forrest Pharmaceuticals. C.C.P. has nothing to disclose. A.T. has nothing to disclose. J.-K.Z. participates on lecture bureaus for Eli Lilly Co., and Forrest Pharmaceuticals.
Supported in part by grant K23RR017043 from the National Center for Research Resources and an investigator-initiated grant from Pfizer Pharmaceuticals Group.
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, MI 48109-0276 (FAX: 734-647-9727; E-mail: ysmith@umich.edu).

symptoms (8, 13), whereas 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 central nervous system, 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 (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 noninvasive 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 in postmenopausal women. We hypothesized that in comparison with the placebo condition, HT would recruit differentially 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 reported previously (23, 25).

MATERIALS AND METHODS

Subjects

As part of an extensive assessment of hormone effects on neural processing, a group of 10 healthy postmenopausal women, 56 to 60 years of age (mean age 56.9 years, SD = 1.4 years), 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, E_2, complete blood cell count, thyroid-stimulating hormone, electrolytes, and liver function tests), and a physical examination including pelvic examination and pelvic ultrasound scan were obtained. All women had normal results of Papanicolaou smears and mammograms within 1 year before participation in the study.

Women were free of significant general medical, neurologic, or psychiatric illness; had not received HT in the last 3 months; had never had 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 >5 mm, ovarian pathologic conditions on ultrasound examination, migraines, liver dysfunction, history of thromboembolic disease, uncontrolled thyroid disease, fasting cholesterol level >300 mg/dL, fasting triglyceride level >300 mg/dL, and fasting glucose level >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 used a randomized, double-blind, placebo-controlled crossover design of HT versus placebo. We chose an available Food and Drug Administration–approved combination HT product. Subjects were randomly assigned to the order they received HT with 5 μg ethinyl E_2 and 1 mg norethindrone acetate (Femhrt; Warner Chilcott, Larne, United Kingdom; provided by Pfizer Pharmaceuticals, New York, NY). Randomization was performed with a computer-generated random number list. Before beginning treatment the subjects had baseline neuropsychological testing. Subjects received HT or placebo for 4 weeks, followed by a 1-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 (28, 29) and presented to subjects through a set of radio frequency–-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 four runs. Each run had a duration of approximately 4 to 5 minutes with a 30-second break between runs.

In each session, blocks of four pictures of each affective state were counterbalanced for a total of 48 pictures per run. Each picture was presented for 3.5 seconds with