History of Major Depressive Disorder and Estradiol Effects on Psychosocial Stress Response and Emotional Episodic Memory

Specific Aims

Major depressive disorder (MDD) is the most prevalent psychiatric disorder[1], with women having a 2-3 times greater lifetime prevalence than men. The factors that contribute to the greater lifetime prevalence of MDD in women are not completely understood. However, the concurrence of increased risk in women with the duration of monthly fluctuations in ovarian hormones (puberty to menopause)[2, 3], suggests that gonadal hormones may contribute to the etiology of MDD in women. Vulnerability to depression, circulating estrogen levels, and altered psychosocial stress response may interact to affect emotional processing and memory. These changes may contribute to cognitive processes involved in major depressive episodes.

Previous studies suggest that stressful events are often important antecedents to depressive episodes[4-6], and that depression history is associated with altered stress responses [7, 8]. Both MDD[9-14] and the response to psychosocial stressors[15-18] have been associated with attention and memory bias toward negative stimuli. Enhanced memory for negative stimuli may reinforce the perception that mild stressors and negative information are of greater salience. These changes in cognitive emotional processes may contribute to and perpetuate depressive episodes. Additionally, MDD is associated with persistent, hyperactive hypothalamic-pituitary-adrenal (HPA) axis function [7, 8]. Trait vulnerability to MDD may be characterized by alterations in the structure and function of brain areas that are important in the response to psychosocial stress.

Altered frontal-limbic functional activity and connectivity have been consistently found in studies of both currently depressed [19-27] individuals and those in remission[28-30]. These neuroanatomical differences may represent trait biomarkers for depression. However, these depression-related characteristics have not been previously examined in relation to the mood effects of estradiol and psychosocial stress.

The postmenopausal stage represents a naturally occurring period of stable, low circulating ovarian hormones in which to investigate the effects of estradiol, separate from those of progesterone. Previous studies of the interaction of estradiol administration and psychosocial stress in healthy postmenopausal women suggest that estradiol enhances negative mood following psychosocial stress [31]. However, trait vulnerability to depression may alter the effects of estradiol, such that the interaction with psychosocial stress may be very different in women with and without a previous history of depression.

The proposed study will investigate whether a past history of MDD modulates the effects of estradiol on brain activity associated with the response to psychosocial stress, and the effects of stress and estradiol on episodic emotional memory retrieval in women. Two groups of postmenopausal women will be recruited, with and without a personal history of MDD. All women will receive three months of estradiol. Psychosocial stress response will be assessed during a laboratory psychosocial stress task using functional magnetic resonance imaging (fMRI). Emotional episodic memory retrieval following psychosocial stress will be tested.

**Aim #1**: Determine how estradiol alters the brain activity patterns during the response to psychosocial stress in women with and without a past history of MDD.

**Hypothesis**: After estradiol women with a past history of MDD will show greater activity in dorsal system structures, and less activity in ventral system structures during psychosocial stress, compared to women without a past history of MDD.

**Aim #2**: Determine whether a past history of MDD interacts with estradiol to modulate the effects of psychosocial stress on emotional episodic memory retrieval.

**Hypothesis**: Women with a past history of MDD will show impaired recognition of positive words compared to women without a past history of MDD. After estradiol and following the stress task, the groups will not differ in performance. The performance differences between women with and without a past history of depression will be related to differences in brain activity patterns during the stress task.
Significance

The purpose of this review is to provide background on previous research and theories that inform the hypothesis that estradiol will differentially affect stress responding and the effects of stress on emotional episodic memory retrieval in postmenopausal women with and without a past history of major depressive disorder. **This review will address four major points:** 1) Estradiol affects the function of brain networks important to emotional processing and mood regulation. The effects of estradiol may be different in women with mood disorders and healthy women. 2) There are changes in stress system function and structure that are characteristic of major depressive disorder. 3) Psychosocial stress has effects on emotional memory that may be related to the cognitive processes underlying depression. 4) There is an overlapping system of brain structures that are important for emotional processing, the stress response, and episodic memory. Changes in these structures may be the mechanism through which estradiol, stress, and depression interact.

Major depressive disorder (MDD) is one of the most prevalent and debilitating psychiatric disorders [1]. 6.7% of the adult US population experience depressive episodes each year[32], and rates are expected to rise over the next 20 years [33]. Antidepressant medications are the first line of treatment for MDD, however approximately 30% of individuals do not experience remission in response to their first antidepressant treatment [34], and efficacy rates decrease with second and third treatment attempts[35]. The lifetime prevalence of MDD in women is nearly twice that in men [2, 36], with increased vulnerability beginning at puberty and lasting until menopause [2, 3]. There are a number of factors that likely contribute to MDD risk, including trait biological factors and stressful life events. Additionally the concurrence of increased rates of depressive episodes in women, compared to men, and reproductive periods during which ovarian hormones fluctuate [36], suggests that gonadal hormones may have a role in depression risk. Understanding the interactions of stress and sensitivity to ovarian hormones in MDD risk will provide important information about the vulnerability to MDD in women, and inform the development of new prevention and treatment strategies for a large portion of MDD patients.

Estradiol Effects on Mood

Although there is some consensus that gonadal hormone fluctuations have effects on mood [37-40], the separate roles and mechanisms of estradiol and progesterone in MDD risk remain to be delineated. Even in healthy women, low estradiol phases of the menstrual cycle are associated with increased symptoms of negative mood [38]. However, most women do not develop mood disorders as a result of these cyclic fluctuations in hormones. A subgroup of women may have vulnerability traits that make them more susceptible to mood perturbations during low estradiol phases of the menstrual cycle. In these women estradiol fluctuations may contribute to depression.

While most women do not develop mood disorders as a result of ovarian hormone changes, the increased risk for first onset depression as estradiol declines during the late perimenopause [39, 41, 42], and the relation of premenstrual dysphoric disorder to the low estradiol phase of the menstrual cycle [43], suggest that some women are susceptible to mood dysregulation as a result of normally low estradiol levels. It may be that the role of estradiol in MDD is characterized by altered brain response to normal circulating levels rather than differences in estradiol levels.

Estradiol has varied effects throughout a number of brain systems, including brain regions important for the autonomic, hormonal, and cognitive-emotional response to psychosocial stress [44, 45]. The relation of stress to depression onset [4-6] and the altered function of the stress system in MDD [7, 8] suggest that modulation of the psychosocial stress response may be a mechanism through which estradiol fluctuation may contribute to MDD risk. Therefore, the effects of estradiol on the psychosocial stress response may be very different in women with and without a previous history of depression.

Stress and Depression

The stress exposure model of depression suggests that MDD is the result of a vulnerability to depression, combined with the trigger of stressful life events [46, 47]. Accordingly, depressive episodes are most often preceded by stressful life events [4, 5, 48]. Altered stress responses, and abnormal function of the brain regions important to the stress response, have been consistently found in individuals with MDD[40]. The system that is involved in the response to stress includes the autonomic nervous system, the hypothalamic pituitary adrenal (HPA) axis, and brain regions that are involved in orchestrating the autonomic, hormonal, and emotional response to the stressor. This system normally serves to ready the body to optimally respond to stressors.

MDD symptoms resemble an unregulated stress response[7], including HPA hyperactivity and insensitivity to negative feedback of the stress hormone cortisol [49]. These findings extend to women with MDD, who have higher basal cortisol levels, and blunted responses to psychosocial stressors than women.
without MDD [8].

Altered HPA function may be especially important in the etiology of MDD in women. Although there is no difference in the number of stressful life events [40], or the perception of these events [50], between men and women, the cortisol response to stress does show sex differences, and decreases during high estradiol phases of the menstrual cycle [51, 52]. Also, women appear to remain more sensitive than men to lower levels of cortisol following repeated stressors [44, 53]. These findings provide evidence that ovarian hormones modulate stress system functioning in women. Periods of increased stress sensitivity, due to ovarian hormone changes, may present windows of vulnerability to mood dysregulation in women who are at risk for MDD.

Men and women also show different brain activity to psychosocial stressors that, in women, is modulated by menstrual cycle [44]. **Women may be more sensitive to mood dysregulation following psychosocial stress than men because of ovarian hormone effects on the HPA axis and brain circuits important for the stress response.** Prolonged emotional processing, following psychosocial stress, with continued cortisol release, may result in mood dysregulation and depression in women with vulnerability to MDD. Indeed, women with MDD have greater HPA axis dysregulation than men with MDD [54, 55], suggesting that the stress system may be particularly important to MDD in women. Estradiol may attenuate sympathetic and HPA axis activity to stress [56-58]. However, the separate effects of estradiol and progesterone remain to be fully delineated.

**Emotional Cognition Changes in Depression**

Although stressful life events [4-6] and altered stress responses [7, 8] are important characteristics of MDD, there are also alterations in emotional and cognitive processes that are associated with depressive episodes [9-14]. Depression is characterized by increased attention and memory for negative information [9, 10, 13], and decreased memory and attention for positive stimuli [14, 59], that remains during remission [29].

Beck’s cognitive model of depression posits that individuals with MDD experience information according to mood congruent schemas, and are apt to interpret information as reflecting a negative self-image, a negative view of external information, and pessimism about the future [60]. The cognitive model of MDD posits that emotional processing circuits in the brain are altered in depression so that there is a bias toward negative information, and attenuated processing of positive information [61]. There may be enduring alterations in emotional cognitive processing that confer continued vulnerability to depressive episodes during remission.

The emotional cognitive changes that are associated with depression are similar to those seen following acute stressors in healthy controls. Stress before episodic memory retrieval decreases performance for both neutral and positive words [15-18]. Dysregulated HPA function in MDD may modulate the effects of acute stress induced cortisol rises on memory and contribute to the cognitive emotional alterations in depression. The effects of estradiol on these processes have not been previously examined and may inform the understanding of the association between stress and MDD in women.

**Shared Neuroanatomical Systems in Mood Regulation, Stress Response, and Episodic Memory**

The similar changes in cognitive emotional processing in depression [9-14] and following acute stressors [7, 8] may reflect shared brain networks for mood regulation, emotional processing, and stress responding. An emerging neuroanatomical model of depression posits mood dysregulation as a result of an imbalance in functional activity in the dorsal and ventral divisions of the limbic system and prefrontal cortex (PFC) [62-64]. The dorsal division includes the hippocampus, dorsal anterior cingulate cortex (dACC), and dorsal lateral prefrontal cortex (dPFC) [62-64]. Structures in the ventral system include the amygdala, ventral/subgenual anterior cingulate (vACC), ventral prefrontal cortex (vPFC), and medial prefrontal cortex (mPFC) [62-64]. The ventral system allows for the rapid appraisal of emotionally valenced stimuli, while the dorsal system provides the capacity to modulate the affective and physiological consequences of ventral output [65]. Greater activity in ventral system structures and less activity in dorsal structures in response to negative stimuli has been a consistent finding in MDD, compared to healthy controls [63, 64]. Dysfunction in these systems, or their interaction, may result in vulnerability to mood disorders.

The dorsal and ventral systems also have roles in the response to psychosocial stress [66-68] and emotional cognitive tasks [69, 70]. HPA axis response to psychosocial stress is associated with increased activity in ventral system structures, paired with decreased activity in the dorsal system [71]. Alterations in these structures may contribute to cognitive difficulty and negative bias in MDD. The interaction of stress and depression may be examined through the activity of these structures. Altered structure and function in brain regions, that are indicated in both stress responses and emotional cognitive processes, may contribute to enhanced responding to stressful life events. These changes may result in negative bias in memory and confer vulnerability to depression.

The brain regions that are commonly indicated in studies of MDD and in recent neuroimaging studies of
Psychosocial stress are important targets for investigating vulnerability to MDD and the interaction with stressful life events. That these same regions are responsive to estradiol manipulation [72-75] is interesting in light of the mood effects of estradiol in both healthy women [38], and women with mood disorders related to ovarian hormone fluctuations [39, 41, 42]. High endogenous estradiol and exogenous administration are associated with reduced ventral system responses to negative stimuli [73, 74]. Estradiol administration, following low estradiol, increases resting activity in dorsal system regions [41]. Although these studies suggest that estradiol attenuates emotional processing and supports mood regulation, the effects of estradiol remain unclear in women with a past history of MDD, in whom the ventral and dorsal structures may be altered.

There is an overlapping system of brain regions that function in mood regulation, the response to psychosocial stress, and episodic memory. These systems are altered in MDD, and sensitive to estradiol effects in healthy women. The effects of estradiol on the brain regions involved in the response to stress and emotional processes may be particularly important in women who have alterations in these systems that make them vulnerable to MDD. In women with MDD vulnerability, estradiol may support normal function of these systems, while having little or opposite effects for women in whom these systems are already functioning optimally. Periods of low estradiol may represent windows of risk to depressive episodes, in women with a previous history of MDD, because of differential effects of estradiol on mood regulation, stress, and episodic memory systems. Understanding the interactions of vulnerability to MDD, stress, and estradiol, and how this differs between women with and without a past history of depression will be important for developing more efficacious prevention and treatments for women with MDD.

**Approach**

30 postmenopausal women will be characterized as having a personal history of MDD or no personal history of MDD. The subjects will participate in one baseline session, which will include an MRI session to assess brain structure, regional brain resting activity, and cerebral blood flow, as well as an emotional episodic memory task. All women will receive three months of oral estradiol. Each subject will then complete one post treatment session, which will include structural and functional MRI and an emotional episodic memory task. Examining postmenopausal women allows for relatively constant levels of other ovarian hormones and the isolation of the effects of estradiol.

**Subjects:** Experimental subjects will consist of 30, non-smoking, post-menopausal women (age 50-75). Subjects will have no current Axis I disorders and no MRI contraindications. Half of the subjects will have a past personal history of MDD.

**Medical Screening:**

Subjects will be physically healthy without menses for at least 1 year, have an follicle stimulating hormone (FSH) level greater than 30 mIU/ml, be nonsmokers, have a normal mammogram within the last year, and without surgically-induced menopause (bilateral oophorectomy). They will not be taking hormone therapy, or oral contraceptives, and will be at least one year without such treatment. Subjects will have a body mass index less than 33 kg/m². Subjects will be assessed by history, physical exam, and routine laboratory tests and will be examined by a nurse-practitioner/physician’s assistant to establish general physical health and for specific physical contraindications for estradiol therapy or MRI.

**Cognitive/Behavioral Screening:**

All subjects will be cognitively and behaviorally assessed using: the Wechsler Abbreviated Scale of Intelligence (WASI) [76], the Mini Mental State Exam (MMSE) [77], Brief Cognitive Rating Scale [78], and the Mattis Dementia Rating Scale [79] to establish a Global Deterioration Scale score (GDS) [80]. Subjects will be required to have a GDS score of 1-2 and a MMSE score of greater than or equal to 27. Subjects will be excluded if they score below 123 on the Mattis scale or a score less than 90 on the WASI.

**MDD History Screening:**

Participants will be screened for current and past depression, mania and dythymia using the partial Structured Clinical Interview for DSM-IV-TR (SCID) [81] to establish the presence/absence of Axis I psychiatric disorders, the Beck Depression Rating Scale, and the Beck Anxiety Inventory (BAI) [82]. Participants who meet criteria for a history of PMDD on the Composite International Diagnostic Interview for premenstrual dysphoric disorder (CICI-PMDD) will be excluded. Criteria for never depressed subjects will include a current score less than 7 on the BDI, current score...
less than 15 on BAI, and no current or past episodes that meet SCID criteria for MDD, dysthymia, or mania. Criteria for prior history of MDD will include at least one episode, in the last ten years, that meets criteria for MDD on the SCID, with no MDD episodes in the last year, current BDI score less than 7, and current BAI less than 15. These criteria are similar to those used in previous studies that found activity pattern [83] and structural differences [84, 85] between currently depressed, remitted depressed, and never depressed subjects, suggesting that these criteria are sensitive and specific enough to separate these subject groups.

Family history information will be collected in a face to face interview with the subject using a modified semi-structured family history assessment module (Family Instrument for Genetic Studies) [86]. Each subject will have a blood sample drawn for individual serotonin transporter gene promoter (5HTTLPR) genotyping, which has been reported to correlate with vulnerability to mood disturbance [87]. These results in will not be used as criteria for study inclusion, or for subject group, but will be used to correlate with the emotional episodic memory and fMRI data.

Hormone Treatment:

Each subject will be placed on estradiol oral preparation containing 17β-estradiol (Estrace) at a dose of 2.0 mg/day (1 mg for the first month and 2 mg for the following 2 months). We utilize this pattern of estradiol administration to avoid estradiol-related side effects, e.g. breast tenderness. Three months of estradiol administration at this dose has been found to be sufficient in our prior studies to produce significant behavioral and cognitive treatment differences [31]. After the completion of the Stress Study Day, subjects will be administered progesterone (Provera) 10 mg per day for 12 days to produce endometrial shedding. Plasma FSH, estradiol, and testosterone levels will be measured at both the baseline and Stress Study Day visits.

Study Timeline

Aim #1

The aim of this phase of the experiment is to determine whether a past history of MDD alters the estradiol effects on the response to acute psychosocial stress in postmenopausal women. Following three months of estradiol, both subject groups will return for the stress study day, during which they will undergo the MIST task. Brain activity during the MIST will be measured with fMRI.

MIST:

The Montreal Imaging Stress Task (MIST) is a computer-based task that has been designed for the imaging environment. The subject is presented with arithmetic problems and is instructed to complete the problems as quickly as possible. There are three task conditions presented pseudo-randomly during the MIST: 1) “Rest” condition consists of the task screen with no problem presented 2) “Control” condition, the subject is presented with arithmetic problems and instructed to solve the problems as quickly as possible 3) “Experiment” condition, there is a time limit for each problem that is represented by a moving blue bar and subjects are presented with information about their performance compared to average user performance on a green, yellow, and red bar. The MIST induces psychosocial stress through the experience of poor performance in the face of the expectation of high performance and social evaluative threat, provided through scripted investigator feedback. Previous studies utilizing the MIST have shown that the combination of the computer based performance challenge and investigator interaction induces moderate psychosocial stress [66, 67, 71]. MIST reactivity will be assessed post hoc through cortisol measurements (see below).
The MIST will be run in a block design with activity measured over the temporal length of each condition, and averaged to give mean activity related to the task condition. Each condition is repeated twice within a task run, and there are three runs so that there are six blocks of each condition. Comparing the “Control” condition and the “Experimental” condition will control for brain activity associated with doing the arithmetic task, and allow for the separation of activity related to the stress response. The “Rest” condition presents a 30 second break for the subject. This protocol has been designed with the developers of the MIST, and is similar to protocols used in previous studies by the developers and their collaborators. Subjects will be acclimated to the MRI environment by use of an MRI simulator.

Neuroendocrine and Autonomic Assessment:

Stress responding to the MIST will be assessed through cortisol measurements. Free salivary cortisol will be measured through oral swabs placed under the tongue. Saliva samples will be collected at regular intervals throughout the Stress Study Day to allow for the determination of an area under the curve for cortisol response to the MIST. Autonomic measures of stress reactivity will also include galvanic skin response (GSR) and heart rate variability (HRV) as measured through MRI compatible telemetry instruments. These measures are used to assess HPA and autonomic function during stress responding [51, 52, 66-68, 88-90].

Subjective Measures:

The subjective response to the MIST will be assessed by the Stress Arousal Checklist (SACL)[91] and Profile of Mood States (POMS) [92] before and after the MIST. Additionally, following the MIST, subjects will complete a visual analogue scale for rating of task perception, including effort and stressfulness of the task [93]. These scales will provide measures of stress, arousal, and mood before and after the MIST.

Data Analysis

Statistical parametric mapping using a general linear model approach will be used for a whole brain fMRI analysis. All of the images from each task condition will be averaged for each subject to create a mean image for the contrast “Experimental/ Control” for each subject. The block of each condition will be modeled as a box-car function and convolved with the canonical hemodynamic response function to model the expected blood oxygen level dependent (BOLD) signal change across conditions. These contrast images will then be used for second level multi-subject/between group analyses. These contrast images will be further analyzed using standard analysis of variance (ANOVA) procedures.

The subjective measures will be analyzed using a mixed model, repeated measures ANOVA. The analysis will be a 2X2 ANOVA, with MDD history as the between subjects factor, and time (before and after MIST), as the within subjects factor.

Interpretation and Limitations:

The hypothesis that estradiol decreases brain activity related to stress responding only in women with a past history of MDD will be supported by greater dorsal system activity and less ventral system activity, during the MIST, after three months of estradiol in women with a personal history of MDD, compared to women with no personal history of MDD.

One limitation of this study is that there is no placebo condition. The time and resources for this study preclude the inclusion of a true placebo condition, however the contrast of interest in this study is between the subject groups and the difference between women with and without a previous history of MDD. The primary aim of this study phase is to determine the differences in brain activity to psychosocial stress, in combination with estradiol effects, between women with and without a past history of MDD. Future studies may include a placebo condition to delineate the separate effects of estradiol and the stress manipulation.

A second possible limitation to this study is that estradiol replacement in postmenopausal women may alter regional cerebral blood flow (CBF) [94]. All subjects will undergo pseudo-continuous arterial spin labeling (PCASL) and resting fMRI during the baseline visit and at the stress study day, following three months of estradiol. Resting fMRI allows for the measurement of activity while subjects are awake but not actively engaged in a task. PCASL allows for the measurement of CBF. These measures will be included to assess whether estradiol has effects on CBF, or resting activity, that may be related to brain activity patterns during the MIST.

Aim #2

The aim in this phase of the experiment is to determine whether a past history of MDD alters estradiol effects on psychosocial stress and emotional episodic memory processes and retrieval. Both subject groups will
complete an emotional episodic memory task at the baseline visit and at the stress study day, following three months of estradiol. The emotional episodic memory task will consist of an encoding and recognition phase.

During the encoding phase, subjects will be presented with 30 words for study (10 neutral, 10 positive, and 10 negative). The study words will be taken from the Affective Norms for English Words (ANEW) list, which provides a set of normative emotional ratings, including valence and arousal, for a large number of words in the English language[95]Words will be of medium frequency of occurrence [96], and high concreteness [97, 98]. Two different sets of words will be created that will be counterbalanced across testing days. During the encoding task, subjects will be instructed to read the words out loud, to ensure that they read each word, and to try to remember the words for later testing.

During the recognition phase, subjects will be presented with a combination of the 30 words that were presented during the encoding phase, and 30 new words that were not presented during the encoding task. Subjects will be asked to press a button to indicate whether the word is an old word that they had seen previously or a new word. The new words will be matched on frequency and concreteness to the studied words. Measures of sensitivity, bias, and reaction time will be obtained from the behavioral performance of this task. The effects of cortisol administration [15, 16] and acute laboratory stress [15, 99, 100] on emotional memory encoding and consolidation have been studied using similar protocols.

On the baseline day the encoding and recognition phases will be separated by the MRI session, during which subjects will undergo about one hour of scanning, including a control task for the MIST. The control task will consist of the “Control” condition of the MIST task and a similar protocol for neuroendocrine, and autonomic measurements as the stress study day. During the stress study day, the encoding and recognition phases will be separated by the MRI session, which will last about one hour, and include the MIST and neuroendocrine and autonomic measurement protocol. The control task for the MIST, during the baseline session, will allow for a similar period of time between the encoding and recognition phases on each day, and will ensure that subjects are engaged in similar activities during consolidation, with the difference between the two days being the stress condition of the MIST.

Data Analysis
Performance on the emotional episodic memory task will be calculated by d’, a measure of sensitivity in detecting hits and false alarms. Retrieval performance will be analyzed using a mixed model, repeated measures ANOVA. The analysis will be a 2X2 ANOVA, with MDD history as the between subjects factor, and time (baseline and Stress Study Day), as the within subjects factor.

Interpretation and Limitations:
Previous studies suggest that the baseline performance, before estradiol, should differ between the two subject groups, with women with a past history of MDD having worse recognition for positive compared to negative words. However, this finding has never been tested in postmenopausal women. The hypothesis that estradiol reduces the effects of psychosocial stress on emotional episodic memory only in women with a past history of MDD will be supported by poorer performance for recognition of positive words in subjects with a past history of MDD at the baseline visit, and no difference between the subject groups in recognition performance for positive words at the stress study visit, following 3 months of estradiol. Additionally, recognition performance for positive words following the MIST and after 3 months of estradiol should be related to the brain activity patterns during the MIST in both subject groups. Recognition performance for positive words should be related to activity in the DLPFC and hippocampus during the MIST.

Again, one limitation of this study is that there is no placebo condition, and the separate effects of stress and estradiol on emotional episodic memory cannot be delineated. However, the between subjects contrast is the primary comparison of interest and will provide important information about the difference in the combined effects of estradiol and stress in women with and without a previous history of MDD.

The interaction of estradiol, depression history, and stress on emotional cognitive processes has not, to my knowledge, been previously examined. Although I expect to replicate the previous findings in younger subjects[17, 18], this experiment will provide insight into this area of research even if these previous results are not extended to postmenopausal women. If there is no difference in performance for the recognition of positive words between the subject groups before estradiol, that would suggest that reduced memory for positive stimuli, which has been consistently found even in remitted depressed subjects [29], may not persist into the postmenopause. Whether estradiol affects recognition performance after psychosocial stress in either subject group remains an important question which may provide information about the effects of estradiol in the postmenopause.
References