EFFECT OF HORMONE REPLACEMENT THERAPY ON IMPLICIT AND EXPLICIT MEMORY IN POST-MENOPAUSAL WOMEN

A Thesis Presented to the Faculty
of
California State University, Stanislaus

In Partial Fulfillment
of the Requirements for the Degree
of Master of Arts in Psychology

By
June M. Newman
May 2014

CERTIFICATION OF APPROVAL

EFFECT OF HORMONE REPLACEMENT THERAPY ON IMPLICIT AND EXPLICIT MEMORY IN POST-MENOPAUSAL WOMEN

by
June M. Newman

Signed Certification of Approval Page is on file with the University Library

Dr. Harold Stanislaw Professor of Psychology	Date
Dr. Dawn Strongin Professor of Psychology	Date
Dr. Victor X. Luevano Associate Professor of Psychology	Date

DEDICATION

To Henry Gustav Molaison who gave 50 years of his life to memory research and his brain, post mortem, to future memory research.

ACKNOWLEDGEMENTS

Any undertaking is a collaboration, not only of those directly involved, but also of those who indirectly inspired and supported the effort. As such, many deserve acknowledgement for their contributions to this project. First and foremost, I would like to express my deep personal and professional gratitude to my thesis chair, Dr. Harold Stanislaw. He was an exceptional advisor throughout the entire undertaking, with just the right balance of allowing me the independence I needed in order to gain from the process and support to get me through the rough patches. His expertise in statistics was invaluable in getting the project over the finish line. I am especially grateful that he was willing to take on this project twice. His dedication to and interest in research is an inspiration that reaches far beyond the scope of this work. I thank him, not only for the original inspiration to undertake this line of inquiry, but also for fueling the fire of curiosity to continue to ask important questions and look for empirical answers.

Dr. Dawn Strongin was also an inspiration to me. The commonality of our interests and her enthusiasm for the subject made the work enjoyable. Her passion for the brain mirrors my own, although her depth of knowledge and expertise is far greater. I am grateful for how freely and generously she shared that knowledge. Dr. Victor Luevano had the arduous task of refreshing my memory for experimental design and statistical procedures. I am thankful for his patience and never-ending willingness to help further my understanding. Although I never thought I would say

it, I am grateful that he made me “explain it to grandma”—a set of conversations that were always challenging, but resulted in a much better grasp of the concepts. His expertise in the area of hormones and behavior was also instrumental in completing this project. As a whole, I am grateful to have benefited from the support and encouragement of such an exceptional group of scholars. Any shortcomings in the study cannot be attributed to the committee members, as those inadequacies are entirely my own.

There is a small group of people whose day-to-day work may go unacknowledged even though it is vital to the completion of any work of this sort. For me, these unsung heroes include Julie Rueben, the interlibrary loan coordinator and Galdina Serrano, the graduate secretary for the psychology department. Julie’s response to interlibrary requests was amazingly fast—it often seemed to happen within the blink of an eye. The timeliness of her response certainly contributed to the relatively quick completion of this project. Galdina had all the answers to my every question regarding the details of the process—regardless of how minute that question might be. Her patience did not escape my notice. Lastly, I would like to acknowledge someone who has long since retired, but was always a bright spot in the department, Marji Petersen.

I would also like to thank all of the women who agreed to be participants in the study. They generously gave of their time and shared many personal details. Their contribution cannot be overstated for without them, this study would not have been possible. It was a privilege to connect with so many vibrant, resilient, and

inspiring women. Lee Kooler and Becky Ganes were early mentors in my journey through the domain of psychology. They have remained close friends over the years and their support contributed greatly to the completion of the study. Last, but certainly not least, I would like to acknowledge my family and friends. The depth of my gratitude here is endless and beyond words. As Oprah Winfrey noted, "Lots of people want to ride with you in the limo, but what you want is someone who will take the bus with you when the limo breaks down." I am humbly grateful to them for unhesitatingly jumping on the bus with me.

TABLE OF CONTENTS

PAGE

LIST OF TABLES

ABSTRACT

The present study looked at the effect of hormone replacement therapy (HRT) on implicit and explicit memory test performance in post-menopausal women ($N = 60$). Women who were either on HRT ($n = 20$), had previously been on HRT ($n = 20$), or had never been on HRT ($n = 20$) were recruited from local residents of Stanislaus, San Joaquin, Sacramento, and Tuolumne counties. Explicit memory was measured using the Logical Memory subtest of the Wechsler Memory Scale. Implicit memory was measured using one of four stem completion tests that were counterbalanced across conditions and used low-frequency words. It was hypothesized that the HRT group would outperform the previous-HRT and non-HRT group on both tests. Results fully supported the hypothesis. A significant negative correlation was noted between age and implicit, but not explicit, scores. These findings suggest that HRT may have useful role in enhancing explicit and implicit memory in post-menopausal women.

REVIEW OF LITERATURE

As humans age, the potential for decline in cognitive functioning often becomes a concern. A change in memory is one of the first areas in which individuals may notice this decrease in functioning and for many, this may be the most disconcerting change in cognitive abilities. Memory is vital for effective functioning, not only in daily living, but also in all areas of cognition (Robinson-Riegler & Robinson-Riegler, 2012). Although age-related changes may be a source of discomfort for some, they become an even greater concern for women as they approach menopause. With the onset of menopause, women face major hormonal changes not experienced to the same degree in the male aging process. This hormonal shift will affect many areas of their lives.

The dramatic drop in estrogen that accompanies menopause has an impact on many other physical systems besides the reproductive system. Along with the loss of the ability to bear children, women may lose valuable bone density and the natural protection that this hormone offers against cardiovascular disease (Marieb, 2000). Research also suggests that, with lowered levels of estrogen, a woman may experience a greater decline in cognitive functioning than her male counterpart (Juraska & Rubinow, 2008; Phillips & Sherwin, 1992; Sherwin, 2006; Sherwin & Henry, 2008). As the largest generational cohort in the United States thus far, the aging of the Baby Boomers means that a larger number of women will be dealing with these changes.

Estrogen Uses and Effects

The use of exogenous estrogen to ameliorate the effects of menopause goes back many decades. Early use in the 1930's focused on alleviating uncomfortable symptoms of menopause rather than disease prevention. In the years since, hormone replacement has been touted to have a wide number of uses, including: reversing menopause and retaining one's femininity, preventing wrinkles and other physical signs of aging, staving off depression, as well as helping with the prevention of more serious medical concerns such as heart attack, stroke, and Alzheimer's disease (Zandi et al., 2002). With the FDA approval of hormone replacement therapy (HRT) for the treatment of osteoporosis in 1986, preventative medical use steadily increased and—with off-label use—broadened in scope (Boston Women's Health Book Collective, 2006).

In the 1970's, HRT began losing some of its early shine as a cure-all for age-related changes and menopausal maladies. A number of studies found a possible link between exogenous estrogen use and endometrial cancer, raising concerns about the negative effects that may result from HRT (Cramer & Knapp, 1979). Due to these risks, progesterone (or the synthetic form, progestin) was added to HRT formulations to be used in women who had not undergone surgical menopause. Results from the Heart and Estrogen/Progestin Replacement Study (HERS) study (Hulley et al., 1998) and the Million Women Study (Beral et al., 2003), along with the early termination of the Women's Health Initiative (WHI) study in 2002, cast additional serious concerns on the safety of HRT use in post-menopausal women.

Concerns about increased stroke, cardiac disease, and breast cancer raised by the WHI study were well publicized in the mainstream media. In spite of this, women may not have had a clear understanding of the WHI study outcomes. A phone survey of 670 female Kaiser members who were users of HRT was conducted by Ettinger, Grady, Tosteson, Pressman, and Macer (2003) to determine the impact that WHI study results had on women's decisions about using HRT. They found that although a large number (93%) of the women surveyed reported knowing about the new findings, only 57% considered the information to be sound regardless of whether the source of their information was from the media, health care providers, or their health plan administrators. In spite of the high level of awareness of new outcomes from the WHI study, only 23% of the women surveyed were correct in their understanding of the results; 64% did not know what the study had found, 7% were not sure, and 6% were incorrect about the study findings. However, 56% of the women surveyed indicated that they had wanted to stop using HRT in the months following the WHI report. Of these, 79% reported that health information about the study from mass media had influenced them to make that decision. Of the 44% continuing on HRT, relief from vasomotor and mood symptoms, prevention of osteoporosis, and better bladder control were deciding factors.

Doctors responded to the WHI findings almost immediately. HRT using the estrogen/progestin combination dropped 46% and estrogen-only formulas dropped by 28% within five months after the discontinuation of the WHI study (Buist et al., 2004). In the years following its termination, many critics of the WHI study have

questioned the validity of the findings (e.g. Bluming & Tavris, 2009; Gleason, Carlsson, Johnson, Atwood, & Asthana, 2005; Horgervorst, 2013; Ostrzenski & Ostrzenska, 2005). Even so, over the past decade the use of HRT has continued to show a steady decline (Stagnitti & Lefkowitz, 2011; Steinkellner et al., 2012). Toward the end of 2013, *JAMA* featured a 13-year follow-up to the WHI study with the conclusion that "Menopausal hormone therapy has a complex pattern of risks and benefits" (p. 1353). From a clinical standpoint, the recommendations by Manson et al. (2013) were for conservative use, bringing HRT full circle—appropriate in the short-term for managing menopausal symptoms, but not chronic disease. From a researcher's perspective, noting the complexity of the picture throws open a wide door for further research and better understanding.

Estrogen and Memory

The WHI study contained within it a number of smaller studies looking at different variables. One of these subsets was the Women's Health Initiative Memory Study (WHIMS). Utilizing the double-blind, randomized, placebo-controlled, long-term design of the WHI study, the WHIMS focused on the potential of HRT to reduce dementia in older women (Shumaker et al., 1998). After the early termination of the study, the U.S. Department of Health and Human Services National Institutes of Health issued a statement announcing that results from the WHIMS indicated:

> Older women taking hormone therapy had twice the rate of dementia, including Alzheimer's disease (AD), compared with women who did not take the medication…. The study also found that combination therapy did not

protect against the development of Mild Cognitive Impairment (2003, para. 1 & 2).

No research study is without its drawbacks, and criticisms that can be reasonably levied at the WHIMS include: the advanced age and health of the women in the WHIMS (who were all over 65 years old, many with other serious health issues); the use of only one administration route and dosing level of the proprietary combination of estrogen/progestin Prempro™;[1] and the use of only one cognitive measure (the Modified Mini-Mental State Exam) that may not have fully assessed verbal memory (Sherman, 2005). In spite of the WHIMS findings, estrogen has been found in a number of studies to have a positive effect on verbal memory and cognitive functioning, as outlined below.

Resnick et al. (2006) reported on findings from the WHI Study of Cognitive Aging (WHISCA), an ancillary study of the WHI study and WHIMS. As a subset, participant profiles (n = 1,416), dosage and administration of Prempro™, and study design mirrored the WHIMS. Unlike the WHIMS, a broader range of cognitive assessments targeting specific cognitive abilities was used. Annual testing, controlling for repeated measures effects, was done over a 2½ year period—WHISCA study data were collected up to the day before the premature termination of the WHI. The WHISCA findings suggested a selective positive effect of HRT, favoring figural memory over verbal memory. In the area of verbal memory, the WHISCA findings suggested a detrimental effect of HRT, similar to that found in the

[1] This arm of the WHI study was sponsored by the manufacturer of Prempro™, Wyeth Pharmaceuticals.

WHIMS. Of course as a subset of the WHIMS (Shumaker et al., 1998), the same criticisms can be applied to the WHISCA study. Additionally, the WHISCA was planned as a 4-year study and the early termination may have affected the results.

A meta-analysis of epidemiological (correlational) and experimental HRT studies on cognitive functioning by Hogervorst, Williams, Budge, Riedel, and Jolles (2000) noted the inconsistencies in HRT effects across studies, with larger effects in epidemiological studies than in experimental studies. Overall, only 45% of all tests of cognitive functioning showed a positive effect of HRT. To address reports that HRT has a selective effect on cognitive functions, memory tests were compared with non-memorial tests of cognitive functioning. Positive effects of HRT were found in 48% of memory tests compared to 47% for non-memorial tests, with the remaining 52% and 53%, respectively, showing no effect. Memory tests were further divided into verbal memory tests and non-verbal tests of memory. With this division, 43% of verbal memory tests showed a favorable effect of HRT, compared with only 21% of non-verbal tests of memory. Interestingly, the only memory test that showed an undisputed positive effect of HRT was the paragraph recall test. Variability in the findings across studies may be due to age differences and length of time since onset of menopause, length of HRT use, differences in types and dosages of HRT, and the health status of the participants. Potential confounds included the expectancy effect, healthy user effect, physician bias in prescribing HRT, and inaccuracies in self- or surrogate-reports of HRT use. Two of the findings were particularly interesting:

Women with low education seemed to benefit more from HRT, and the least effective drug was Prempro™ (after controlling for socio-economic status).

A decade later, with the debate about HRT effects on women's cognition still going strong, Hogervorst and Bandelow (2010) reported the results of another meta-analysis of HRT treatment trials. Considering the divergent findings of non-human animal studies (to be discussed later) and clinical trials, this analysis looked at 38 clinical studies using blinded, randomized, and controlled trials. The strongest effects were found in the area of verbal memory, with 26% of studies showing a negative effect and 37% showing a positive effect (37% were neutral). They also found no support for the "critical period" hypothesis—that administration of HRT during a specific period is critical for the treatment to be of any benefit. Additionally, potential confounds related to the age of the participants and their test performance during the studies were not well supported. Interestingly, the four studies using fMRI found positive effects of HRT 100% of the time, although behavioral measures in these studies often did not support fMRI results.

For example, Shaywitz et al. (1999) reported their findings using fMRI to test the effect that estrogen has on brain activation patterns during working memory tasks. This study was a randomized, double-blind, placebo-controlled crossover trial involving 46 postmenopausal women between the ages of 33 and 61 years. During the first treatment phase the women were administered either 1.25 mg per day of conjugated equine estrogens (CEE) or a placebo for 21 days. This was immediately followed with a 14-day washout period. After the washout period, crossover

treatment of either CEE or placebo was given for another 21 days. Participants were randomly assigned to either the CEE or placebo starting condition. Brain activation patterns were measured using fMRI, during tasks that involved both verbal and nonverbal working memory. A forced choice recognition test was used. The verbal stimuli were a series of pronounceable nonsense words, and the nonverbal stimuli were Tamil letters, which are complex geometric patterns. Although the results showed significant increases in brain activation patterns for the estrogen group, there were no actual increases in the behavioral component of the memory tasks.

Joffe et al. (2006) also used fMRI in a randomized, double-blind, placebo-controlled study of peri- and postmenopausal women (screened for depression) to determine the effect of HRT and symptomatic vasomotor relief on specific cognitive domains. Baseline measures of the California Verbal Learning Test (CVLT), Wechsler Memory Scale-Revised (WMS-R), and the Rey-Osterreith Complex Figure Test were compared, using the same measures, after 12 weeks of treatment. Although 52 women took part in the study, fMRI scans were taken on only 11 women at baseline and post-treatment. During the scans, the participants were asked to perform spatial and verbal memory tasks.

Although Joffe et al. (2006) did not find any significant differences between the HRT and placebo conditions on any of the cognitive tests, they did note that women in the HRT condition made significantly fewer errors of perseveration on the CVLT than women in the placebo condition—a 43% reduction compared to 9% reduction in error, respectively. Results from the fMRI indicated significantly greater

activation in the medial frontal, paracentral frontal, and postcentral gyri of the parietal lobe during the verbal memory task in the women on HRT. During the spatial task, the women on HRT showed greater activation in the superior frontal gyrus, as well as the anterior and posterior cingulate, than women receiving the placebo. In conclusion, Joffe et al. suggested that HRT selectively enhances certain aspects of executive functioning and that relief from certain vasomotor symptoms (hot flashes, but not sleep) may improve cognitive functioning.

Resnick, Maki, Golski, Kraut, and Zonderman (1998) looked at the effects of HRT on regional cerebral blood flow (rCBF) patterns and cognitive performance. Their participants were women over the age of 55 years, who were already participating in a longitudinal neuroimaging study as part of the Baltimore Longitudinal Study on Aging. The women were either users or nonusers of HRT. The two groups were matched on age, education, and vocabulary test scores. Comparisons between the two groups were evaluated using magnetic resonance imaging (MRI), positron emissions tomography (PET), and several neuropsychological assessments. MRI screening showed no significant differences in total brain volume, ventricular volume, lobe volume (frontal, parietal, temporal, and occipital), or volume of gray and white matter between the two groups of women. Baseline measures of rCBf were taken at rest. During subsequent PET scans, the women were asked to perform a verbal memory test and then a figural memory test.

On these tests, Resnick et al. (1998) found that the women on HRT (n = 15) made significantly more correct rejections of incorrect targets than those women not

on HRT (n = 17). The HRT group also showed significantly faster reaction times to verbal stimuli, but slower reaction times to figural stimuli than the non-HRT group. Although significant differences in rCBF were noted between the two groups during each of the tasks, these differences reflected a complex pattern of activations and deactivations when compared to baseline PET scans. Of the 12 neuropsychological assessment tests, the only significant findings were that the HRT group had fewer total errors on the Benton Visual Retention Test (BVRT—a test of short-term figural memory), and increased scores on the short delay-free recall portion of the CVLT (a recall test of verbal targets).

A larger study by Maki, Zonderman, and Resnick (2001) utilized the same Baltimore longitudinal participant pool. In addition to being matched on education and verbal ability, the subset of women participating in this study was also matched on health status and annual income, as well as being screened for symptoms of depression. To increase the likelihood that a cognitively healthy population was being considered, data obtained from women who had developed clinical signs of dementia 5 years post-study were removed from the final analysis. Unlike the previous result from Resnick et al. (1998), the women receiving HRT significantly outperformed those who were not on HRT on verbal learning and memory measures, but not on other cognitive measures. There was a significant age difference between the groups, with an average age of 65 years for participants on HRT (n = 103) and 70 years for those not on HRT (n = 81).

Kampen and Sherwin (1994) also compared healthy postmenopausal women on HRT (n = 28) with women not on HRT (n = 43) using a number of neuropsychological measures. Specific tests of verbal memory included the paragraph recall subtest of the Wechsler Memory Scale, the Selective Reminding Test, and a paired associates test. Participants in the two groups were well matched in the areas of age at testing, age at onset of menopause, educational level, and marital status. A range of dosages, administration routes, and types of HRT were represented and blood draws were used to confirm blood plasma levels of estrogen. Women who were on HRT performed significantly better on the immediate and delayed paragraph recall test than women in the control group. There were no other significant differences between the two groups on any of the other verbal memory measures.

In a more unusual study (Miles, Green, Sanders, & Hines, 1998), an effect of estrogen on memory was found in a group of males preparing to undergo sexual reassignment. Miles et al. looked at the performance of two groups of male-to-female transsexuals: those currently on estrogen therapy (ET), and those waiting to receive ET. Two subtests of the Wechsler Memory Scale were used: the digit span test and the Paired Associates Learning (PAL) test. On the PAL, the men on ET produced higher scores than those not on ET. However, there was no difference in performance between the two groups on the digit span test. The Profile of Mood States (POMS) was used to assess any possible effects of mood state on the scores. Miles et al.

concluded that estrogen might have a selective effect on memory, favoring some types of tests over others.

A study by Kimura (1995) looking at the effect of HRT on various cognitive functions did not find a selective effect. Kimura compared two groups of postmenopausal women: those on HRT (n = 21) and those who were not on HRT (n = 33). All of the women were over the age of 50 years, and were matched on levels of education, age, and scores on an advanced vocabulary test. Ten cognitive measures that typically yield gender differences were used to assess perceptual speed, spatial skills, articulatory and motor skills, verbal fluency, verbal reasoning, and verbal memory. The verbal memory test was a test of explicit memory requiring free recall of a list of 10 unrelated words. This study also used the POMS to control for any possible effects of mood. The results of the study showed that the women on HRT outperformed those women not on HRT on all measures, and that these findings were not due to a difference in affective state between the two groups.

In the interest of greater ecological validity, researchers in New Zealand looked at the effect of HRT on everyday memory tasks. Stephens, Hamilton, and Pachana (2003) used the extended version of the Rivermead Behavioural Memory Test (RBMT-E), an established measure of everyday memory, to assess memory in two groups of healthy post-menopausal women (HRT users and nonusers). Overall, HRT users significantly outperformed nonusers when total scores were compared. HRT users also scored significantly higher than nonusers on the Immediate and Delayed Story Recall subtests, as well as the Messages Delayed subtest. An

interaction effect on the Second Names and Belongings/Appointments subtests was noted, with better memory scores being recorded for older HRT users, but not younger HRT users when compared to non-HRT users of the same age.

The study by Stephens et al. (2003) is of particular interest, not just because of its findings, but also because of the number of sociodemographic variables considered by the researchers. In addition to the usual demographics of age and education, the researchers also recorded self-reports of mood, affect, stress levels, employment status, general health, exercise habits, medications, smoking, and ethnicity. Thorough personal and familial neurological histories, as well as detailed menstrual and menopausal histories, including any vasomotor and pre-menstrual symptoms were recorded for each participant.

Healthy User Effect

Extensive gathering of socioeconomic and health data—as in the Stephens et al. (2003) study—is driven by the desire to address potential sampling biases that are inherent to epidemiological or observational studies. The most common of these is the healthy user effect. This effect is a potential confound whenever one is looking at the effects of preventive therapies, in that individuals who undertake preventive measures are more likely to engage in a number of other behaviors that contribute to a healthy lifestyle. Healthier users are noted to have higher socioeconomic status and education levels; healthier lifestyle choices around smoking, alcohol use, diet, and exercise; better functional and cognitive health; greater inclination toward and accessibility to preventive health care; increased awareness of health issues and

motivation to address those issues; as well as better adherence to medical treatment and less severe disease. Mathews, Kuller, Wing, Meilahn, and Plantinga (1996) found that women who chose to use HRT were significantly healthier before treatment than women who did not elect to use HRT.

Although the healthy user effect may be referred to by a number of different names, such as healthy adherer effect, frailty bias, physician selection bias, or compliance bias, the underlying construct is the same (Majumdar, 2007). Adequately controlling for these effects can be difficult, if not impossible, in observational studies (Majumdar, 2007; Shrank, Patrick, & Brookhart, 2011). Although randomized controlled trials (RCTs) offer the best chance of controlling for healthy user effects, Shrank, Patrick, and Brookhart (2011) suggest changes to traditional study designs and groups, more extensive measuring and analysis of extraneous variables, and the use of additional unrelated diagnostic tests for greater control in non-RCT studies.

In an attempt to develop a predictive model of the healthy user bias, Gleason, Dowling, Friedman, Wharton, and Asthana (2012) looked at 48 variables that could be used to identify potential HRT users. Their analysis isolated nine variables as potential predictors to control for healthy user bias: ethnicity, waist-to-hip ratio, annual household income, self-esteem, autonomy, use of calcium supplements, number of physical exams/year, diabetes, and number of prescriptions. Although promising, further research needs to validate these findings before they can be reliably used.

The change in HRT use patterns subsequent to the termination of the WHI study offers a unique opportunity to look at the healthy user effect in a different population. Previously, women who fit the healthy user profile would be more likely to be HRT users. Post-WHI, women who were on HRT, but no longer use HRT, may now be the healthy users—and of particular interest in the effort to control for this effect.

Explicit and Implicit Memory

Current theories of memory suggest that long-term memory (LTM) involves two different types of memory stores: Explicit memory, also known as declarative memory; and implicit memory, which may also be referred to as nondeclarative or procedural memory (Squire & Zola, 1996). Explicit memory involves the conscious recollection of a previous experience along with the ability to verbalize or declare that recollection, whereas implicit memory is facilitated without conscious recollection or awareness and consequently cannot be acknowledged verbally (Roediger, 1990; Schacter, 1987; Shimamura, 1986). Traditionally, explicit memory has been measured directly through recall and recognition tasks. Measuring implicit memory is more complicated, requiring less direct methods that often involve priming (Roediger, 1990; Schacter, 1992).

The covert nature of implicit memory is not the only complicating factor in finding ways to measure it. Current theoretical models propose several different types of implicit or nondeclarative memory: (a) simple classically conditioned responses, further divided into emotional responses and skeletal responses; (b)

nonassociative learning, such as habituation and sensitization; (c) procedural learning involved in learning skills and habits; and (d) priming and perceptual learning (Squire, 2004). Each of these learning modes may be evidenced in a number of different ways, from the conditioning of eye blink responses to the improvement in an individual's performance in a sport or on a musical instrument as he or she moves from novice to expert.

Researchers have come up with a number of methods to quantify implicit memory. Harvard University's *Project Implicit*® (2011) utilizes an online version of the Implicit Association Test to look at a number of implied associations that may color everyday social interactions and personal perceptions. Initially, this online test harnessed the power of the Internet to gather data for research into how certain implicit associations may underlie the tendency to negatively stereotype. It has now grown to include research projects measuring how implicit associations may affect self-esteem, body perceptions, and anxiety. Other tests used in research on priming and perceptual learning include the lexical decision task, artificial grammar learning, and word-fragment completion or word-stem completion tasks. Of these, the most commonly used implicit measures are the word-fragment completion or word-stem completion tasks (Robinson-Riegler & Robinson-Riegler, 2012).

Word-fragment completion or word-stem completion tasks involve priming. Priming relies on the use of a priming mechanism—a previously presented stimulus—to increase the likelihood of responding correctly on the memory task (Tulving & Schacter, 1990). In a stem completion task, participants are presented

with a list of words to view, but not asked to memorize them. Later, a test comprised of target words from the previously presented list is given to the participants. The test only contains a few letters of the target word—the *stem* or *fragment*—along with a series of blank spaces indicating the remaining number of letters, and their position, in the target word. For example, a stem completion task for the word "sample" would be presented as sa_ _ _ _ . In a word-fragment completion task, the word to be filled in may appear as sa_pl_ or s_mp_ _. Without prompting them to use words from the presented list, the participants are then asked to complete the word by filling in the blanks. In these tests, the priming mechanism serves to facilitate the completion of the target correctly, even without conscious awareness.

One of the first studies to show evidence for a dissociation between explicit and implicit memory using a word-stem completion task was conducted by Warrington and Weiskrantz in 1970. In response to their observations that some patients who had anterograde amnesia showed improvement in their ability to perform certain tasks, Warrington and Weiskrantz considered that this improvement suggested some memorial facilitation of task performance. In two different experiments, Warrington and Weiskrantz looked at memory performance in four patients with amnesia: One had amnesia that was due to a temporal lobectomy, while the remaining three patients had Korsakoff's syndrome. Comparison groups (different for each experiment) consisted of neurological patients with no known memory deficits. The amnesiac and comparison groups were matched on age and intellectual level.

The first experiment by Warrington and Weiskrantz (1970) involved presenting the word stimuli in various degrees of fragmentation, beginning with the most degraded stimulus and working up to the non-fragmented version of the word. In this experiment, three memory tests were used: recall, recognition, and word fragment *recognition* (not word-fragment *completion*). The second experiment presented the words to be learned in a traditional reading format. For this experiment, an additional implicit memory test, a word-stem completion task, was added. In both experiments, the comparison group outperformed the amnesiac group on the explicit memory tests of recall and recognition. However, on the implicit memory tests, the amnesiac group's performance was comparable to or better than the performance of the comparison group. In Experiment 1, there was no significant difference between the groups on the word fragment task. On the stem completion test (Experiment 2), the amnesiac group significantly outperformed the comparison group.

Level of processing has also been shown to affect performance on explicit and implicit memory tasks. The levels of processing model of memory (Craik & Lockhart, 1972) proposes that cognitive processing of material to be remembered occurs at varying levels, ranging from shallow to deep. According to this model, deeper processing, such as the semantic processing of words, leads to increased retention in memory. In a 1991 study, Jelicic and Bonke found a significant effect of processing level in both free recall and word completion tests. Performance was facilitated when the stimulus words were encoded semantically, rather than in a nonsemantic manner on both types of tests

Modern memory research is often thought to have begun in 1957 with the investigation into the severe memory deficits of a patient who became known as H.M., and was the post-temporal lobectomy patient in the aforementioned Warrington and Weiskrantz (1970) study. H.M.'s profound anterograde amnesia (along with some retrograde amnesia), subsequent to a bilateral medial temporal lobectomy undertaken to control epileptic seizures, provided the first documented biological link between specific brain structures and behavioral measures of memory in a living person (Pinel, 1997). As in the case of H.M., neurobiology may help provide evidence for two distinctive memory systems. Advancements in imaging techniques using PET scans and fMRI offer glimpses into neurological activity accompanying various memory tasks, often in real time (Squire, 2009).

Aging and Memory

Anecdotal evidence suggests that memory deficits are unavoidable as one ages. Popular humor abounds with jokes leveled at memory losses experienced with the passing years. With the aging of the Baby Boomers, such jokes are relatable for a greater number of people. While aging is inevitable, severe decline in memory is not. Although the normal aging process includes a gradual atrophy of the cerebrum due to neuronal pruning, remaining intellectually, socially, and physically active can mitigate the detrimental effects that may accompany these changes (Erikson, et al. 2011; James, Wilson, Barnes, & Bennett, 2011; Shimamura, 1996). Currently, research suggests that there is a great deal of variability in memory ability in healthy

aging—ranging from preserved or even increased memory performance to significant decline or deficit in memory ability (Zacks & Hasher, 2006).

There are a number of biological changes that occur throughout the brain as it ages. Changes that may impact memory in the healthy aged include: expansion of cerebral ventricles; deceases in cerebral volume—particularly in the hippocampal regions, the entorhinal cortices, and the inferior temporal cortex; and loss or dysfunction in neuronal synapses (Jellinger & Attems, 2013; Raz & Rodrigue, 2006). For those with amnestic mild cognitive impairment (aMCI)—mild cognitive impairment with memory loss as the primary complaint—there are even greater losses in hippocampal volume, along with reductions in the lateral temporal and parietal areas (Hänggi, Streffer, Jäncke, & Hock, 2011). Petersen et al. (2006) found that patients with aMCI had more neurofibrillary tangles in the hippocampus and entorhinal cortices of the medial temporal lobes (MTL) than age-matched healthy controls. They suggested that the spread of these abnormalties to other areas of the brain coincides with the shift from a diagnosis of aMCI to Alzheimer's disease.

There has been much research into the effect of aging on implicit and explicit memory. Light, Singh, and Capps (1986) used word-fragment completion and word recognition tests to measure implicit and explicit memory, respectively, in younger and older adults. Their findings showed that explicit memory performance declines with age, whereas implicit memory performance remains at a stable level. However, Chiarello and Hoyer (1988) found that there was some decline in implicit memory in older adults. Subsequent research supports the idea of a preserved implicit memory

function and a decline in explicit memory function (Fleischman et al., 2004; Mitchell, 2003; Russo & Parkin, 1993; Schacter, Cooper, & Valdiserri, 1992).

Biological Considerations

Although the hippocampus is often considered the place of memory, consolidation of long-term memories in the brain cannot be tidily attributed solely to one region. It is currently thought that memory is processed and distributed across many areas of the brain. The hippocampus does play a major role in that it is vital to the consolidation of workable or useable memories (Robinson-Riegler & Robinson-Riegler, 2012). Everyday references to memory usually refer to explicit memory. The primary areas of interest for this type of memory are found in the MTL and the diencephalon. Along with the hippocampus, other structures of the MTL believed to be important to the declarative memory process include the rhinal cortices (perirhinal and entorhinal) and the amygdala. Outside of the MTL, the basal forebrain and prefrontal cortex also have roles in the formation of declarative memory (Dworetzky, 2001; Pinel, 1997; Squire, 2009).

The medial diencephalon includes the thalamus and hypothalamus which are both important to memory. Functioning as a routing station for all cognitive processes, the thalamus routes sensory information to the cerebral cortex. The entorhinal cortex serves a similar function in the MTL, routing information from the hippocampus to the neocortex (Dworetzky, 2001; Manns & Eichenbaum, 2006). Specific fields within the hippocampus, the dentate gyrus, along with areas 1 and 3 of

the cornu ammonis (CA1 and CA3), have been a focus of interest in memory studies, particularly in nonhuman animal studies.

The MTL, while important for declarative memory, does not appear to be involved in nondeclarative types of memory. Brain structures supporting implicit memory seem to vary with each of the types. Studies of eyeblink conditioning have noted that this type of classical conditioning involves a cerebellum-hindbrain circuit (Manns & Eichenbaum, 2006). Although simple classical conditioning of skeletal responses is attributed to the cerebellum, classical conditioning of emotional responses appears to be mediated by the amygdala. Nonassociative learning occurs in reflex pathways. The corpus striatum is an important area for the improvement and retention of skills and habits. Implicit memory for perceptual learning and priming is associated with neocortical areas and the caudate nucleus (Dworetzky, 2001; Squire, 2009).

Research findings support theories of memory proposing that distinctly different areas of the brain may be involved during implicit and explicit memory tasks. Using PET scanning techniques, Squire et al. (1992) looked at regional brain activation patterns in normal participants during both a stem completion task and a recall task. Squire et al. found that during the recall task, increased activity was recorded in the areas of the right hippocampus and the right prefrontal cortex. During the stem completion task, there was no activation of the hippocampal region. However, activation of the visual association cortex was present in the PET scans.

Nonhuman animal studies also offer support for two distinctive memory systems. Packard, Hirsh, and White (1989) compared the performance of three groups of rats on two different maze tasks: those with bilateral lesions of the caudate nucleus, those with bilateral lesions of the fimbria-fornix, and an intact control group. The maze task conditions were labeled "win-shift" and "win-stay." The behaviors required for each task were arranged to model declarative memory and "habit" memory, respectively. Rats with caudate lesions were impaired on the win-stay (habit) task, but not on the win-shift task. Rats with fornix lesions were impaired on the win-shift (declarative memory) task, but not on the win-stay task.

As mentioned earlier, the hypothalamus also plays a role in memory. This sexually-dimorphic structure of the diencephalon is also critical to the regulation of reproductive behavior through releasing hormones, particularly gonadotropin releasing hormone which controls the release of gonadal or sex steroids. These sex steroids are produced by the testes in males and the ovaries in females and have various receptor sites throughout the body. Estrogens are a class of ovarian steroids that includes estrone, estradiol, and estriol. Different estrogens are dominant during different stages of the female lifespan. Estrogenic activity during the reproductive years is primarily driven by estradiol. This class of hormones has two known types of receptors, ERα and ERβ. Early research into estrogen receptors in the brain focused on the hypothalamus and pituitary gland. However, through the use of increasingly sophisticated labeling techniques, ERα and ERβ sites have also been found in the brain stem, midbrain, hippocampus, and the cerebral cortex (McEwen, 2002).

Current research suggests that estrogens act locally to enhance memory in the hippocampus, specifically in the pyramidal cells of the CA1 and CA3 areas of the ventral hippocampus (e.g., Isgor & Sengelaub, 1998; McEwen, et al., 2001; Packard & Teather, 1997b; Spencer, et al., 2008; Wolley, 1998). It has been suggested that the mechanism of estrogen-enhanced memory lies in a synergistic interaction that occurs between estradiol and acetylcholine, a neurotransmitter (Packard, Kohlmaier, & Alexander, 1996; Packard & Teather, 1997a,b). An estrogenic effect resulting in an increase in the number of dentate gyri neurons in rats was found by Tanapat, Hastings, Reeves, and Gould (1999). Increased estradiol levels have also been shown to increase the density of dendritic spines in the hippocampus (Wolley, 1998; Wolley, Gould, Frankfurt, & McEwen, 1990; Wolley & McEwen, 1994). These spines are the postsynaptic site for excitatory input to the pyramidal cells and, along with their N-methyl-D-aspartate (NMDA) receptors, have an important role in the associative nature of long-term potentiation (Carlson, 1999). Resnick, Maki, Golski, Kraut, and Zonderman (1998) also suggest that estrogen has a more generalized effect on brain structure by modulating cerebral blood flow and enhancing brain metabolism of glucose. This general effect may account for a positive effect of estrogen on areas of the brain that have not yet been found to have specific receptors for estrogen—such as those involved in implicit memory.

Although the results from studies looking at the effect of HRT on memory are equivocal, there is some support for a positive effect of HRT on memory, particularly explicit verbal memory. Less research has looked into the effect of HRT on implicit

memory. Very little research has compared the effects of HRT on explicit *and* implicit memory. Nonhuman animal research on the effect of estrogen on the brain and behavior offers more evidence for a positive estrogenic effect. It has also been instrumental in identifying biological evidence supporting that effect. Additional research in this area is needed to provide a clearer picture of the effect of HRT on memory. The potential of HRT to protect or enhance memory offers a benefit that could help ease the inevitable aging process for many.

The present study was designed to look at the effect that estrogen might have on explicit and implicit memory tasks. The results of a pilot study (Newman, 2001) indicated a positive effect of HRT on implicit memory tasks, but not explicit memory tasks. Based on the literature, HRT should have had a positive effect on explicit memory as well. It was originally thought that this failure could be attributed to a ceiling effect for the explicit test. However, recent research (Maki, Rich, & Rosebaum, 2002) has also shown a selective effect of estrogen on explicit and implicit memory, with the positive effects of estrogen favoring implicit memory tasks.

Given these findings, the results of the pilot study were reconsidered using a more sensitive measure for the explicit memory task. The original study used a recognition test for the explicit memory measure and a stem completion test to assess implicit memory. The present study used a free recall test rather than a recognition test as the measure of explicit memory. The implicit memory test remained the same, as it proved to be a sensitive measure in the earlier study. In the wake of the WHI

study, it was thought that adding an additional group of participants made up of women who previously used HRT, but no longer do so, would be informative, as the healthy-user effect would now reside in this group. It was hypothesized that HRT would have a positive effect on memory, enhancing performance on the implicit test and the explicit test.

METHOD

Participants

Participants were 60 postmenopausal women between the ages of 40 and 89 years (M = 61.48 years, SD = 9.36 years), recruited from Stanislaus, San Joaquin, Sacramento, and Tuolumne counties. Haphazard and snowball sampling methods were used for recruitment. Of these women, 20 were on HRT (M = 57.45 years, SD = 6.93 years, range = 40 to 71 years), 20 had previously been on HRT (M = 65.15 years, SD = 9.62 years, range = 53 to 85 years), and 20 had never been on HRT (M = 61.85 years, SD = 9.99 years, range = 51 to 89 years). Education levels of the participants ranged from those who had completed high school to those who had earned a Master's degree (see Table 1). Their participation was voluntary and they received no compensation. Each participant was required to sign an informed consent form (see Appendix A). All of the participants were treated in accordance with the "Ethical Principles of Psychologists and Code of Conduct" (American Psychological Association, 2002).

Table 1

Education level percentages by group

Education Level	HRT	Previous HRT	Non-HRT
High school	10%	5%	20%
Some college	30%	35%	15%
AA	15%	20%	20%
BA	35%	20%	30%
MA	10%	20%	15%

Materials and Measures

Wechsler Memory Scale Subtest

The fourth edition of the Wechsler Memory Scales (WMS-IV; Wechsler, 2009) is an individually administered, norm-referenced, and standardized scale used to measure memory in individuals ranging in age from 16 years to 90 years. The scale is divided into an "Adult" battery, designed for use with populations ranging in age from 16 to 69, and an "Older Adult" battery for populations aged between 65 and 90. The Adult battery comprises seven subtests (six primary and one optional) with five indices. The Older Adult battery has six subtests (five primary and one optional) covering four indices. The WMS-IV is a well-researched measure with a high-degree of reliability and validity (Cassady, Dacany, & Chittooran, 2010). For the purposes of this study, only the Logical Memory subtest (LM) was used.

Logical Memory Subtest

The LM is a paragraph recall test of explicit verbal memory. It measures free recall of a narrative immediately after an auditory presentation (LM I), and again after a 20 to 30 min delay (LM II). Story B from the WMS-IV LM subtests was used because it is common to both the Adult and Older Adult batteries and noted to be "directly comparable across all age levels" (Wechsler, 2009). The story contains 25 specific points or "story elements," each of which the participant must recall to obtain score credit for the item. The immediate and delayed raw scores are the sum of the number of items remembered by the participant during immediate and delayed recall, respectively.

Word-list stimuli

Two lists of low frequency words were created, List A and List B. All of the words were nouns or verbs, six or seven letters in length, with a frequency of less than 8.31 occurrences in a corpus of one million English words (Francis & Kucera, 1982). Low frequency words were used because priming has been shown to be more sensitive to low frequency words than high frequency words (Jacoby & Dallas, 1981). Each list contained 20 words and was randomly divided into two sublists of 10 target words each. The sublist from the presented list was used to provide target words for the implicit memory task (see Figure 1). Distractor words for the implicit memory tasks were taken from the alternate word list (the unpresented sublist). See Appendix B for words used in each list.

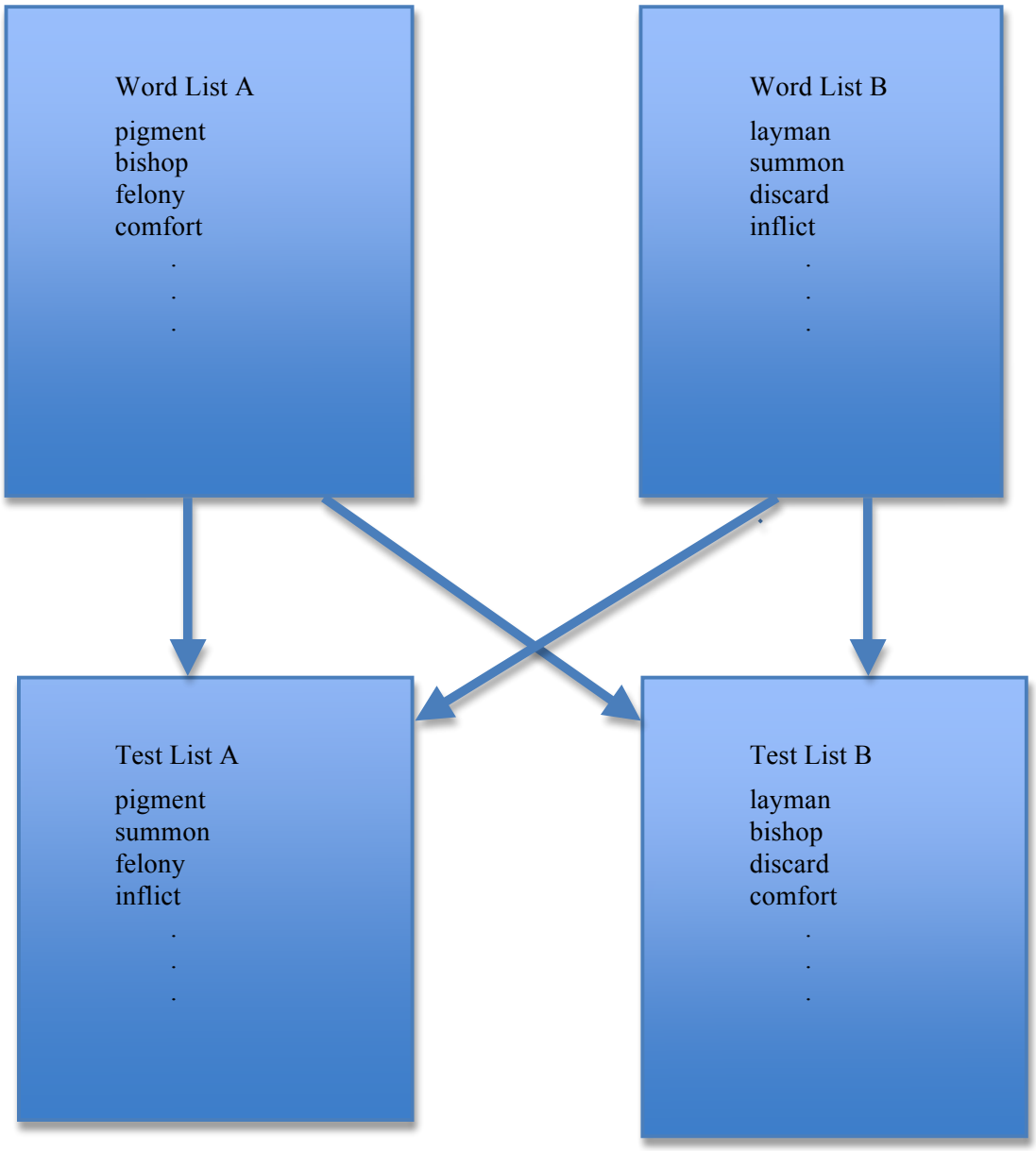

Figure 1. Method of test construction for the stem-completion tests showing how words from each list were divided and distributed between the tests.

Stem Completion

A stem completion test was used to measure implicit memory task performance. It consisted of 10 target words from the presented word list and 10 distractor words from the unpresented list. All of these words were listed in random

order on a single sheet of paper. The first two letters of each word was provided, followed by a series of underlined, blank spaces to indicate the number of remaining letters in the word. Each of the letter pairs forming the word stems was unique in that the pair was not duplicated within the test, although several possible solutions could be generated for each stem. The participant was required to fill in each blank space with the appropriate letter. Two tests were constructed from each word list, one for each set of 10 target words. Each of the four tests was used equally often across each of the HRT conditions. A sample of this test is included in Appendix C.

Filler Tasks

The Differential Emotions Scale (DES; Izard, Dougherty, Bloxom, & Kotsch, 1977) was used as a filler task between the study phase and the testing phase. The DES is a 30-item, self-report measure. It uses a 5-point Likert scale to assess 10 different emotions and takes approximately 10 min to complete. An additional 15 min was spent completing a biographical interview between the implicit tests and the LM delayed recall test. See Appendix D for a copy of the data collection form.

Procedure

Post-menopausal women were prescreened for their HRT status and separated into three groups: those who had never been on HRT; those who were currently on HRT; and those who had previously been on HRT, but were no longer on HRT. For the purposes of this study, HRT was defined as any medically prescribed formula of estrogen replacement, including estrogen and progestin combinations. Forms of alternative HRT, such as herbal or naturopathic remedies, were not considered to be

HRT, although any use of such products was noted in the participant's biographical data. All of the women were also checked for sufficient visual and auditory acuity to ensure that they could adequately ascertain the presence of the various stimuli on the presentation apparatus.

For all of the sessions, prescreening was followed by: (a) 3MMSE prompting with three words to remember (orange, sock, and truck); (b) an auditory presentation of the paragraph material to be recalled; (c) a test of immediate recall for the paragraph; (d) visual presentation of one of two word lists; (e) administration of the mood scale; (f) an interview to collect biographical data; (g) administration of the implicit memory test; (h) the delayed recall for the paragraphical material presented 20 to 30 min earlier; and finally, (i) recollection of the 3MMSE prompts. HRT status was a between-subject variable and word list was a within-subject variable. The two word lists (A and B) were constructed so that words were used as either targets or distractors equally often within each group. Although participants could not be randomly assigned to the HRT, previous HRT, or non-HRT condition, the word lists were randomly assigned. The order of testing, immediate recall, implicit memory, and then delayed recall, remained the same for each participant. Each participant was presented with the stimuli and tested individually. All of the participants were told that the purpose of the study was to look at the effect of words on mood.

Auditory presentation of the Logical Memory Test (LM) paragraph was done on an Apple iPad 3rd generation using the Voice Pad program from 10Pearls. Participants were prompted for the first free recall of the LM immediately after this

presentation. Visual presentation of the word list for the stem completion task was also done on an Apple iPad 3rd generation using the Flashcards [+] program from NKO Ventures. Each word was displayed on the computer screen at a rate of 3 s per word. Visually presented verbal stimuli have been shown to result in better priming (Rajaram & Roediger, 1993). The words were presented in random order during each session. During the session, the participants were told that a series of words would appear on the screen, that they should say the word out loud, and then state whether the word was happy, neutral, or sad. The mood association was used to ensure a deeper level of processing.

Immediately following the word list presentation, participants were asked to complete the DES. After this filler task was completed, the participants were asked to fill out the stem completion test as quickly and completely as possible. Rapid performance was emphasized in order to limit the use of explicit memory during this test. As soon as the participants had finished the stem completion test, they spent 15 min in a face-to-face interview to complete the biographical data. Once the biographical interview was complete and 20 to 30 min had passed since the presentation of LM paragraph, the LM delayed free recall test was given. Upon completion of this final test, the participants were debriefed. The debriefing statement can be found in Appendix E.

Data Analysis

Raw data were compiled into three separate scores: (a) implicit target, (b) implicit distractor, and (c) explicit. Each score represented the total number of items matching the criteria for that score. The stem completion test was scored by totaling the number of correctly completed target words and the number of correctly completed distractor words. In order to be considered correct, each word had to have the correct letter placed in the correct position. The proportion of correctly completed distractor words was used as a baseline measure and subtracted from the proportion of correctly completed target words. This score was labeled "implicit."

Raw scores, rather than scaled scores, were used to assess performance on the explicit memory measures: "LM I" for immediate recall and "LM II" for delayed recall. The immediate recall score (LM I) represents the total number of story elements correctly recalled immediately after the presentation of the story. The delayed recall score (LM II) indicates the number of story elements correctly recalled after a 20 to 30 min delay. The raw scores from LM I and LM II were added together and the total was converted to a proportion of correctly remembered story elements. This score was labeled "explicit."

A MANOVA with preplanned orthogonal contrast testing was used to compare the three groups of women on the two memory measures. A one-way ANOVA was used to compare age differences between the groups. Scores on the four implicit tests were also compared using a one-way ANOVA. Pearson's correlation was used to assess relationships between age, quality of the previous night's sleep,

and quantity of the previous night's sleep on the explicit and implicit scores. Spearman's rho was used to determine correlates of the educational level variable. An alpha level of .05 was used for all statistical tests.

RESULTS

Raw scores for the explicit test ranged from 9 to 39 out of a possible 50. Raw scores for the implicit test ranged from 0 to 3 for target words and 0 to 2 for distractor words. On this test, the maximum possible in each category was 10. See Appendix F for a cross tabulation of raw implicit scores. All raw scores were converted to proportions for comparison. Descriptive statistics for each group can be found in Table 2. There were no significant differences between the four implicit tests, $F(3, 56) = 0.80$, $p = .50$. All of the women remembered the three items from the 3MMSE. However, six women required categorical reminding for one item in order to remember it. Four of these women were from the group previously on HRT and two women were from the group never on HRT. Overall, there was a significant effect of HRT on the memory tests, $\lambda = .66$, $F(4, 112) = 6.41$, $p < .001$, $\eta_p^2 = .19$. Orthogonal contrasts indicated that women currently on HRT scored .15 higher on the explicit test ($p < .001$) and .07 higher on the implicit test ($p = .01$) than women who were previously on HRT and women who had never been on HRT. There were no significant differences on the memory tests between those who had previously been on HRT and those who had never been on HRT (ps > .21).

Table 2

Means, standard deviations, and confidence intervals for explicit and implicit scores

	Explicit			Implicit		
HRT Status	*M*	*SD*	95% CI	*M*	*SD*	95% CI
Current HRT user (n = 20)	.54	.12	[.49, .59]	.14	.10	[.09, .18]
Previous HRT user (n = 20)	.41	.11	[.36, .47]	.06	.08	[.01, .10]
Never used HRT (n = 20)	.37	.13	[.31, .42]	.08	.10	[.03, .12]

The results of a one-way ANOVA indicated that there was a small, but significant difference in ages between the groups, $F(2, 57) = 3.72$, $p = .03$, $\omega^2 = .08$. Post-hoc pair-wise comparisons using Tukey's test determined that women in the HRT group were significantly younger than women in the previous-HRT group (p = .02). There were no other significant differences in age between the groups (see Table 3).

Table 3

Age characteristics of each group

HRT Status	*M*	*SD*	95% CI	Minimum	Maximum
Current HRT user (n = 20)	57.45	6.93	[54.21, 60.69]	40	71
Previous HRT user (n = 20)	65.15	9.62	[60.64, 69.66]	53	85
Never used HRT (n = 20)	61.85	9.99	[57.17, 66.53]	51	89

Additional correlational analysis revealed a significant negative relationship between age and implicit test scores. Other than the expected positive correlation between amount and quality of sleep, there were no other significant relationships between the variables. The correlation matrix is presented in Table 4.

Table 4

Means, standard deviations, and intercorrelations for biographical data and test scores

		Correlation (*r*)				
Measure	*M* ± *SD*	1	2	3	4	5
1. Age	61.48 ± 9.36					
2. Educational level	3.00 ± 2.00	.08				
3. Hours of sleep	6.68 ± 1.69	.08	.09			
4. Quality of sleep	3.55 ± 1.00	.11	.11	.54**		
5. Explicit	.44 ± .14	-.02	.03	.13	.21	
6. Implicit	.09 ± .10	-.36*	-.03	-.13	-.21	.22

Note. The educational level correlations were calculated using Spearman's rho. For this variable, median and interquartile range are reported instead of the mean and standard deviation.
*p = .01.**p < .001.

Given the significant age difference between the groups a multiple regression was used to compare the relationship between the HRT status contrasts and age on each dependent measure. The regression equation predicted explicit test scores significantly better than chance, R = .55, $F(3, 56) = 7.91$, $p < 001$. Current HRT use was a significant predictor of explicit test scores after controlling for HRT status and age, B = .05, $t(59) = 4.69$, p = .01. The regression equation also predicted implicit test scores significantly better than chance, R = .44, $F(3, 56) = 4.40$, p = 01. Current HRT use was also a significant predictor of implicit test scores after controlling for HRT status and age, B = .02, $t(59) = 2.03$, p = .05. Thus, the younger mean age of current HRT users cannot fully explain their better performance on the implicit memory test.

DISCUSSION

It was hypothesized that HRT would have a positive effect on memory, enhancing performance on the implicit test and the explicit test. The results of the present study uniformly support the hypothesis. The HRT group performed significantly better on the explicit and implicit memory tests than the previous-HRT and non-HRT groups. Results from the present study replicate the implicit memory findings of the earlier pilot study (Newman, 2001). Unlike the earlier study, the present study did find a positive effect of HRT on explicit memory. As noted by Hogervorst et al. (2000), the paragraph recall test proved to be an effective measure for explicit verbal memory. Changing the explicit measure from a recognition test to one using free recall of paragraphical material allowed for a more sensitive measure of explicit memory performance in the present study.

Paragraph recall tests also were used in the Kampen and Sherwin (1994) study and the New Zealand study by Stephens et al. (2003). Explicit memory results from the present study support the findings of these two earlier studies. The present findings also support the positive effect of HRT on verbal recall found in the 1998 study by Resnick et al. and Kimura's 1995 study. However, the present findings conflict with those of Resnick et al. (2006) in the WHISCA study. Resnick et al. found that HRT did not have a positive effect on verbal memory, and suggested that HRT may have a detrimental effect on verbal memory.

The present findings also add to the already extensive body of research begun in the 1970's by Warrington and Weiskrantz supporting the theoretical model proposing two separate LTM stores (Roediger, 1990; Schacter, 1987; Shimamura, 1986). Much research on explicit and implicit memory has also looked into how each of those memory stores holds up in older populations. Everyday wisdom—or common sense—may lead one to think that it seems reasonable to assume that any preservation or decline of memory would be consistent for explicit and implicit memory; however research does not always support this assumption. Early research by Light et al. (1986) found evidence that indicated implicit memory does not decline the way explicit memory does, whereas Chiarello and Hoyer (1988) found that there is a decline only in implicit memory with increasing age. Although subsequent research (Fleischman et al., 2004; Mitchell, 2003; Russo & Parkin, 1993; Schacter et al., 1992) supported a preservation of implicit memory with age, the present findings do not support that view.

The present study found a significant negative correlation between age and implicit memory scores. The relationship between age and explicit scores was also negative, but not significantly so. Although the negative relationship between age and explicit memory scores was not significant, it may be that age had just as much of an impact on explicit memory as on implicit memory, but the explicit decline was masked by the strategies the participants adopted. Anecdotally, many women in the study shared that they had used specific memory strategies to remember the prompts for the 3MMSE, such as "The truck wore orange socks." It may be that the

participants were using similar strategies to help them remember story elements from the explicit measure. Indeed, during the debriefing, many women shared that they had surmised early on that it was a study of memory.

Conversely, none of the participants indicated that they had made the memory connection for the implicit test. Even if they had, the covert nature of implicit memory precludes the use of any helping strategies to mitigate implicit memory deficits that may occur during the aging process. In retrospect, the benefits of screening for memory impairments may have been outweighed by the introduction of a potential confound. In future studies, it may be informative to conduct a post-session survey inquiring about the use of memory strategies. At the very least, including a simple yes-no question about the use of memory strategies would help control for this potential confound.

A cursory review of the results from the present study suggest that the healthy-user effect is not a confounding variable in studies on estrogen and memory. As suggested by Ettinger et al. (2003), it was thought that the healthy-user would be the women in the previous-HRT group. Indeed, all of the women in this group indicated that they had stopped HRT due to health concerns, greater personal susceptibility to publicized risk factors, or—as indicated by Buist et al., (2004)—at the behest of their physician due to the health risks. The findings in this study do not conclusively support the view that previous-HRT users are healthier than HRT users. Although there were no apparent differences in health status between the groups in the present study, it may be that HRT users lead healthier lives than previous-HRT

users. The choice to remain on HRT may be a more informed choice than the decision to stop. Savvy consumers of health information would be aware of the uneven (and occasionally inaccurate) media representations of research, possibly leading them to seek additional information about any health concerns. In future studies, gathering additional information about health practices and lifestyle choices may lead to more conclusive evidence for—or against—the effect of a healthy-user bias.

Maki et al. (2001) found a positive effect of HRT on verbal memory with an HRT group that was significantly younger than the non-HRT group. In the present study, HRT use was a stronger predictor of explicit and implicit memory performance than age. Even though age was not as significant a predictor of memory performance as current HRT use, the significant negative relationship between age and implicit memory scores suggests that age may be an important factor. Future research would benefit from having groups more evenly matched in age. A smaller age range may also improve the informative value of future research. In spite of the challenges in recruiting a pool of participants from this population, controlling for the length of menopause, the length of HRT, and the formulary of the HRT may expand the conclusions that can be drawn from future studies. As always, a larger sample would increase the generalizability of future research findings.

Research to date shows that the role estrogen plays in cognitive functioning is a complex and fascinating one. The results of the present study may offer indirect support for nonhuman animal studies finding a positive effect of estrogen on

memory-related brain structures and biochemistry. Many aspects of this role need to be clarified in order to have a better understanding of how this hormone affects the lives of women. It is important to continue exploring the ways in which estrogen affects the well-being of women and their ability to function at their best, both cognitively and physically. The present research adds to the current body of knowledge about estrogen and memory. Future research in this area is needed to expand the knowledge base for estrogen and its effects in order to elucidate the value of HRT for women.

REFERENCES

REFERENCES

American Psychological Association. (2002). Ethical principles of psychologists and code of conduct. *American Psychologist*, *57*, 1060-1073. doi:10.1037/0003-066X.57.12.1060

Beral, V., & Million Women Study Collaborators. (2003) Breast cancer and hormone-replacement therapy in the Million Women Study. *The Lancet, 362,* 419-427. Retrieved from www.millionwomenstudy.org

Bluming, A. Z., & Tavris, C. (2009). Hormone replacement therapy: Real concerns and false alarms. *The Cancer Journal, 15,* 93-104. doi:10.1097/PPO.0b013e31819e332a.

Boston Women's Health Book Collective. (2006). *Our bodies, ourselves: Menopause*. New York: Simon & Schuster.

Buist, D., Newton, K., Miglioretti, D., Beverly, K., Connelly, M., Andrade, S.,…Kessler, L. (2004). Hormone therapy prescribing patterns in the United States. *Obstetrics & Gynecology*, *104*, 1042-1050. doi:10.1097/01.AOG.0000143826.38439.af

Carlson, N. R. (1999). *Foundations of physiological psychology* (4th ed.). Boston: Allyn & Bacon.

Cassady, J., Dacanay, A., Chittooran, M. M. (2010). Wechsler Memory Scale-IV. In Spies, R. A., Carlson, J. F., & Geisinger, K. F. (Eds.), *The Eighteenth Mental Measurements Yearbook*. Highland Park, N.J. Buros Institute.

Chiarello, C., & Hoyer, W. J. (1988). Adult age differences in implicit and explicit memory: Time course and encoding effects. *Psychology and Aging, 3,* 358-366. doi:10.1037/0882-7974.3.4.358

Craik, F. I. M., & Lockhart, R. S. (1972). Levels of processing: A framework for memory research. *Journal of Verbal Learning and Verbal Behavior, 11,* 671-684. doi:10.1016/S0022-5371(72)80001-X

Cramer, D. W., & Knapp, R. C. (1979). Review of epidemiologic studies of endometrial cancer and exogenous estrogen. *Obstetrics and Gynecology, 54,* 521-526. Retrieved from http://journals.lww.com/greenjournal/toc/1979/

Dworetzky, B. A. (2001). The neurology of memory. *Seminars in Speech and Language, 22,* 96-108. doi:10.1055/s-2001-13934

Ettinger, B., Grady, D., Tosteson, A. N., Pressman, A., & Macer, J. L. (2003). Effect of Women's Health Initiative on women's decisions to discontinue potmenopausal hormone therapy. *Obstetrics and Gynecology, 102,* 1225-1232. doi:10.1016/j.obstetgynecol.2003.08.007

Erickson, K. I., Voss, M. W., Prakash, R. S., Basake, C., Szabo, A., Chaddock, L.,…Kramer, A. F. (2011). Exercise training increases size of hippocampus and improves memory. *Proceedings of the National Academy of Sciences of the United States of America, 108,* 3017-3022. doi: 10.1073/pnas.1015950108

Flashcards [+] (v1.5.1; iPad3,1; iOS 7.1.1) [Computer software]. (2012). NKO Ventures, LLC. Retrieved from http//nkoventuresllc.com

Frances, W. N., & Kucera, H. (1982). *Frequency analysis of English usage: Lexicon and grammar.* Boston: Houghton Mifflin.

Fleischman, D. A., Wilson, R. S., Gabrieli, D. E., Bienias, J. L., & Bennet, D. A. (2004). A longitudinal study of implicit and explicit memory in old persons. *Psychology and Aging, 19,* 617-625. doi:10.1037/0882-7974.19.4.617

Gleason, C. E., Carlsson, C. M., Johnson, S., Atwood, C., Asthana, S. (2005), Clinical pharmacology and differential cognitive efficacy of estrogen preparations. *Annals of the New York Academy of Sciences, 1052,* 93–115. doi:10.1196/annals.1347.007

Gleason, C. E., Dowling, N. M., Friedman, E., Wharton, W., Asthana, S. (2012). Using predictors of hormone therapy use to model the healthy user bias: How does healthy user status influence cognitive effects of hormone therapy? *Menopause: The Journal of The North American Menopause Society, 19,* 524-533. doi:10.1097/gme.0b013e318238ff2c

Hänggi, J., Streffer, J., Jäncke, L., & Hock, C. (2011). Volumes of lateral temporal and parietal structures distinguish between healthy aging, mild cognitive impairment, and Alzheimer's disease. *Journal of Alzheimer's Disease*, *26*(4), 719-734. doi: 10.3233/JAD-2011-101260

Horgervorst, E. (2013). Estrogen and the brain: Does estrogen treatment improve cognitive function? *Menopause International, 19,* 6-19. doi:10.1177/1754045312473873

Horgervorst, E., & Bandelow, S. (2010). Sex steroids to maintain cognitive function in women after the menopause: A meta-analysis of treatment trials. *Maturitas, 66,* 56-71. doi:10.1016/j.maturitas.2010.02.005

Hogervorst, E., Williams, J., Budge, M., Riedel, W., & Jolles, J. (2000). The nature of the effect of female gonadal hormone replacement therapy on cognitive function in post-menopausal women: A meta-analysis. *Neuroscience*, *101*, 485-512. doi:10.1016/S0306-4522(00)00410-3

Hulley, S., Grady, D., Bush, T., Furberg, C., Herrington, D., Riggs, B., Vittinghoff, E. (1998). Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA, 280,* 605-613. doi:10.1001/jama.280.7.605

Isgor, C., & Sengelaub, D. R. (1998). Prenatal gonadal steroids affect adult spatial behavior, CA1 and CA3 pyramidal cell morphology in rats. *Hormones and Behavior, 34,* 183-198. doi:10.1006/hbeh.1998.1477

Izard, C. E., Dougherty, F. E., Bloxom, B. M., & Kotsch, W. E. (1977). The Differential Emotions Scale: A method of measuring the subjective experience of discrete emotions. Princeton, New Jersey: Educational Testing Service.

Jacoby, L.L., & Dallas, M. (1981). On the relationship between autobiographical memory and perceptual learning. *Journal of Experimental Psychology: General, 110,* 306-340. doi:10.1037/0096-3445.110.3.306

James, B. D., Wilson, R. S., Barnes, L. L., & Bennett, D. A. (2011). Late-life social activity and cognitive decline in old age. *Journal of the International Neuropsychological Society, 17,* 998–1005. doi:10.1017/S1355617711000531

Jelicic, M., & Bonke, B. (1991). Level of processing affects performance on explicit and implicit memory tasks. *Perceptual and Motor Skills, 72,* 1263-1266. doi:10.2466/pms.1991.72.3c.1263

Jellinger, K. A., & Attems, J. (2013). Neuropathological approaches to cerebral aging and neuroplasticity. *Dialogues in Clinical Neuroscience, 15,* 29-43. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3622466/

Joffe, H., Hall, J. E., Gruber, S., Sarmiento, I. A., Cohen, L. S., Yurgelun-Todd, D., & Martin, K. A. (2006). Estrogen therapy selectively enhances prefrontal cognitive processes: A randomized, double-blind, placebo-controlled study with functional magnetic resonance imaging in perimenopausal and recently postmenopausal women. *Menopause, 13,* 411-422. doi:10.1097/01.gme.0000189618.48774.7b

Juraska, J. M., & Rubinow, M. J. (2008). Hormones and memory. In J. H. Byrne (Ed.), *Learning and memory: A comprehensive reference* (Vol. 3, pp. 503-520). Atlanta: Academic Press.

Kampen, D. L., & Sherwin, B. B. (1994). Estrogen use and verbal memory in healthy postmenopausal women. *Obstetrics and Gynecology, 83,* 979-983. doi:10.1097/00006250-199406000-00017

Kimura, D. (1995). Estrogen replacement therapy may protect against intellectual decline in postmenopausal women. *Hormones and Behavior, 29,* 312-321. doi:10.1006/hbeh.1995.1022

Light, L. L., Singh, A., & Capps, J. L. (1986). Dissociation of memory and awareness in young and older adults. *Journal of Clinical and Experimental Neuropsychology, 8,* 62-74. doi:10.1080/01688638608401297

Majumdar, S. R. (2007). *The healthy user effect: Ubiquitous and uncontrollable.* Retrieved from http://www.jhsph.edu/research/centers-and-institutes/center-for-drug-safety-and-effectiveness/academic-training/seminar-series/Sumit%20Majumdar.pdf

Maki, P., Rich, J. B., Rosenbaum, R. S. (2002). Implicit memory varies across the menstrual cycle: Estrogen effects in young women. *Neuropsychologia, 40,* 518-529. doi:10.1016/S0028-3932(01)00126-9

Maki, P. M., Zonderman, A. B., Resnick, S. M. (2001). Enhanced verbal memory in nondemented elderly women receiving hormone-replacement therapy. *American Journal of Psychiatry, 158,* 227-233. doi:10.1176/appi.ajp.158.2.227

Manns, J. R., & Eichenbaum, H. (2006). Evolution of declarative memory. *Hippocampus, 16,* 795-808. doi:10.1002/hipo.20205

Manson, J. E., Chlebowski, R. T., Stefanick, M. L., Aragaki, A. K., Roussouw, J. E., Prentice, R. L.,…Wallace, R. B. (2013). Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of

the Women's Health Initiative randomized trials. *JAMA, 310,* 1353-1368. doi:10.1001/jama.2013.278040

Marieb, E. N. (2000). *Essentials of human anatomy and physiology* (6th ed.). San Francisco: Benjamin/Cummings.

Matthews, K. A., Kuller. L. H., Wing, R. R., Meilahn, E. N., & Plantinga, P. (1996). Prior to use of estrogen replacement therapy, are users healthier than nonusers? *American Journal of Epidemiology, 143,* 971-978 doi:10.1093/oxfordjournals.aje.a008678

McEwen, B. (2002). Estrogen actions throughout the brain. *Recent Progress in Hormone Research*, *57*, 357-384.

McEwen, B., Akama, K., Alves, S., Brake, W. G., Bulloch, K., Lee, S….Milner, T. A. (2001). Tracking the estrogen receptor in neurons: Implications for estrogen-induced synapse formation. *Proceedings of the National Academy of Sciences of the United States of America, 98,* 7093-7100. doi:10.1073/pnas.121146898

Miles, C., Green, R., Sanders, G., & Hines, M. (1998). Estrogen and memory in a transsexual population. *Hormones and Behavior, 34,* 199-208. doi:10.1006/hbeh.1998.1478

Mitchell, D. B. (2003). Age Differences in Implicit Memory: Conceptual, Perceptual, or Methodological?. *Psychology and Aging, 18,* 807-822 doi:10.1037/0882-7974.18.4.807

Newman, J. M. (2001). *Effect of Estrogen Replacement Therapy on Implicit and Explicit Memory Tasks*. Unpublished manuscript, Department of Psychology, California State University, Stanislaus, Turlock.

Ostrzenski, A., & Ostrzenska, K. (2005). WHI clinical trial revisit: Imprecise scientific methodology disqualifies the study's outcomes. *American Journal of Obstetrics and Gynecology*, *193,* 1599-1604. doi:10.1016/j.ajog.2005.07.085

Packard, M. G., Hirsh, R., & White, N. M. (1989). Differential effects of fornix and caudate nucleus lesions on two radial maze tasks: Evidence for multiple memory systems. *The Journal of Neuroscience, 9,* 1465-1472. Retrieved from http://www.jneurosci.org/content/9/5/1465

Packard, M. G., Kohlmaier, J. R., & Alexander, G. M. (1996). Post-training intra-hippocampal estradiol injections enhance spatial memory in male rats: Interaction with cholinergic systems. *Behavioral Neuroscience, 110,* 626-632. doi:10.1037/0735-7044.110.3.626

Packard, M. G., & Teather, L. A. (1997a). Post-training estradiol injections enhance memory in ovariectomized rats: Cholinergic blockade and synergism. *Neurobiology of Learning and Memory, 68,* 172-188. doi:10.1006/nlme.1997.3785

Packard, M. G., & Teather, L. A. (1997b). Intra-hippocampal estradiol infusion enhances memory in ovariectomized rats. *Neuroreport, 8,* 3009-3013. doi:10.1097/00001756-199709290-00004

Petersen, R. C., Parisi, J. E., Dickson, D. W., Johnson, K. A., Knopman, D. S., Boeve, B. F.,…& Kokmen, E. (2006). Neuropathologic features of amnestic mild cognitive impairment. *Archives of Neurology, 63,* 665-672. doi:10.1001/archneur.63.5.665

Phillips, S. M., & Sherwin, B. B. (1992). Effects of estrogen on memory function in surgically menopausal women. *Psychoneuroendicrinology, 17,* 485-495. doi:10.1016/0306-4530(92)90007-T

Pinel, J. P. J. (1997). *Biopsychology* (3rd ed.). Boston: Allyn & Bacon.

Project Implicit®. (2011). Harvard University. Retrieved from https://implicit.harvard.edu/implicit/

Rajaram, S. R. & Roediger III, H. L. (1993). Direct comparison of four implicit memory tests. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 19,* 765-776. doi:10.1037/0278-7393.19.4.765

Raz, N. & Rodrigue, K. M. (2006). Differential aging of the brain: Patterns, cognitive correlates and modifiers. *Neuroscience and Biobehavioral Reviews 30,* 730–748. doi: 10.1016/j.neubiorev.2006.07.001

Resnick, S. M., Maki, P. M., Golski, S., Kraut, M. A., & Zonderman, A. B. (1998). Effects of estrogen replacement therapy on PET cerebral blood flow and neuropsychological performance. *Hormones and Behavior, 34,* 171-182. doi:10.1006/hbeh.1998.1476

Resnick, S. M., Maki, P. M., Rapp, S. R., Espeland, M. A., Brunner, R., Coker, L. H., …Shumaker, S. A., for the Women's Health Initiative Study of Cognitive

Aging Investigators. (2006). Effects of combination estrogen plus progestin hormone treatment on cognition and affect. *Journal of Clinical Endocrinology and Metabolism, 91,* 1802-1810. doi:10.1210/jc.2005-2097

Robinson-Riegler, B., & Robinson-Reigler, G. (2012). *Cognitive psychology: Applying the science of the mind.* Boston: Allyn & Bacon.

Roediger III, H. L. (1990). Implicit memory: Retention without remembering. *American Psychologist, 45,* 1043-1056. doi:10.1037/0003-066X.45.9.1043

Russo, R., & Parkin, A. J. (1993). Age differences in implicit memory: More apparent than real. *Memory and Cognition, 21,* 73-80. doi:10.3758/BF03211166

Schacter, D. L. (1987). Implicit memory: History and current status. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 13,* 501-518. doi:10.1037//0278-7393.13.3.501

Schacter, D. L. (1992). Understanding implicit memory: A cognitive neuroscience approach. *American Psychologist, 47,* 559-569. doi:10.1037/0003-066X.47.4.559

Schacter, D. L., Cooper, L. A., & Valdiserri, M. (1992). Implicit and explicit memory for novel visual objects in older and younger adults. *Psychology and Aging, 7,* 299-308. doi:10.1037/0882-

Shaywitz, S. E., Shaywitz, B. A., Pugh, K. R., Fulbright, R. K., Skudlarski, P., Mencl, … & Gore, J. C. (1999). Effect of estrogen on brain activation patterns in postmenopausal women during working memory tasks. *Journal of the*

American Medical Association, 281, 1197-1202. doi:10.1001/jama.281.13.1197

Sherwin, B. B. (2006). Estrogen and cognitive aging in women. *Neuroscience 138,* 1021–1026. doi:10.1016/j.neuroscience.2005.07.051

Sherwin, B. B. (1994). Estrogenic effects on memory in women. *Annals of the New York Academy of Sciences, 743,* 213–230. doi:10.1111/j.1749-6632.1994.tb55794.x

Sherwin, B. B. (2005). Surgical menopause, estrogen, and cognitive function in women: What do the findings tell us?. *Annals of the New York Academy of Sciences*, *1052*(1), 3-10. doi:10.1196/annals.1347.001

Sherwin, B. B., & Henry, J. F. (2008) Brain aging modulates the neuroprotective effects of estrogen on selective aspects of cognition in women: A critical review. *Frontiers in Neuroendocrinology, 2*9, 88–113. doi:10.1016/j.yfrne.2007.08.002

Shimamura, A. (1986). Priming effects of amnesia: Evidence for a dissociable memory function. *The Quarterly Journal of Experimental Psychology. Section A: Human Experimental Psychology*, *38*, 619-644. doi:10.1080/14640748608401617

Shimamura, A. (1996). Unraveling the mystery of the frontal lobes. *Psychological Science Agenda, 9,* 8-9. Retrieved from http://socs.berkeley.edu/~shimlab/ShimBiblio.html

Shrank, W. H., Patrick, A. R., & Brookhart, M. A. (2011). Healthy user and related biases in observational studies of preventive interventions: A primer for physicians. *Journal of General Internal Medicine, 26,* 546–550. doi:10.1007/s11606-010-1609-1

Shumaker, S. A., Reboussin, B. A., Espeland, M. A., Rapp, S. R., McBee, W. L., Dailey, M.,…Jones, B. (1998). The Women's Health Initiative Memory Study (WHIMS): A trial of the effect of estrogen therapy in preventing and slowing the progression of dementia. *Controlled Clinical Trials, 19,* 604-621. doi:10.1016/S0197-2456(98)00038-5

Stagnitti, M.N., & Lefkowitz, D. (2011) *Trends in hormone replacement therapy drugs utilization and expenditures for adult women in the U.S. civilian noninstitutionalized population, 2001–2008* (Statistical Brief #347). Agency for Healthcare Research and Quality, Rockville, MD. Retrieved from http://www.meps.ahrq.gov/mepsweb/data_files/publications/st347/stat347.pdf

Steinkellner, A., Denison, S., Eldridge, S., Lenzi, L., Chen, W., Bowlin, S. (2012). A decade of postmenopausal hormone therapy prescribing in the United States: Long-term effects of the women's health initiative. *Menopause*, *19*, 616-621. doi:10.1097/gme.0b013e31824bb039

Stephens, C., Hamilton, Y, & Pachana, N. (2003). Hormone replacement therapy and everyday memory in mid-aged New Zealand women. *New Zealand Journal of Psychology, 32,* 13-21. Retrieved from http://www.psychology.org.nz/cms_show_download.php?id=662

Spencer, J. L., Waters, E. M., Romeo, R. D., Wood, G. E., Milner, T. A., & McEwen, B. S. (2008). Uncovering mechanisms of estrogen effects on hippocampal function. *Frontiers in Neuroendocrinology, 29,* 219-237. doi:10.1016/j.nlm.2004.06.005

Squire, L. R. (2004). Memory systems of the brain: A brief history and current perspective. *Neurobiology of Learning And Memory, 82,* 171-177. doi:10.1016/j.yfrne.2007.08.006

Squire, L. R. (2009). Memory and Brain Systems: 1969–2009. *The Journal of Neuroscience, 29,* 12711-12716. doi:10.1523/JNEUROSCI.3575-09.2009

Squire, L. R., Ojemann, J. G., Miezin, F. M., Petersen, S. E., Videen, T. O., & Raichle, M. E. (1992). Activation of the hippocampus in normal humans: A functional anatomical study of memory. *Proceedings of the National Academy of Sciences, USA, 89,* 1837-1841. doi:10.1073/pnas.89.5.1837

Squire, L., & Zola, S. (1996). Structure and function of declarative and nondeclarative memory systems. *Proceedings of the National Academy of Sciences of the United States of America*, *93*, 13515-13522. Retrieved from http://www.jstor.org/stable/40931

Tanapat, P., Hastings, N. B., Reeves, A. J., & Gould, E. (1999). Estrogen stimulates a transient increase in the number of new neurons in the dentate gyrus of the adult female rat. *The Journal of Neuroscience, 19,* 5792-5801. Retrieved from http://www.jneurosci.org/content/19/14/5792.full.pdf

Tulving, E., & Schacter, D. L. (1990). Priming and human memory systems. *Science,*

247, 301-306. Retrieved from http://www.jstor.org/stable/2873625

U.S. Department of Health and Human Services, National Institutes of Health News. (2003). Rates of dementia increase among older women on combination hormone therapy. Retrieved from http://www.nih.gov/news/pr/may2003/nia-27.htm

Voice Pad (v1.8; iPad3,1; iOS 7.0.2) [Computer software] (2013). 10Pearls LLC. Retrieved from http://www.10pearls.com/clients/mobile-apps-portfolio/voice-pad

Warrington, E. L., & Weiskrantz, L. (1970). Amnesic syndrome: consolidation or retrieval? *Nature, 228,* 628-630. doi:10.1038/228628a0

Wechsler, D. (2009). Wechsler Memory Scale (4th ed.). Pearson, Bloomington, MN.

Wolley, C. S. (1998). Estrogen-mediated structural and functional synaptic plasticity in the female rat hippocampus. *Hormones and Behavior, 34,* 140-148. doi:10.1006/hbeh.1998.1466

Woolley, C., Gould, E., Frankfurt, M., & McEwen, B. (1990). Naturally occurring fluctuation in dendritic spine density on adult hippocampal pyramidal neurons. *Journal of Neuroscience*, *10*, 4035-4039. Retrieved from http://www.jneurosci.org/content/10/12/4035.long

Wolley, C. S., & McEwen, B. S. (1994). Estradiol regulates hippocampal dendritic spine density via an N-methyl-D-aspartate receptor-dependent mechanism. *Journal of Neuroscience. 14,* 7680-7687. Retrieved from http://www.jneurosci.org/content/14/12/7680.full.pdf

Zack, R. T., & Hasher, L. (2006). Aging and long-term memory: Deficits are not inevitable. In E. Bialystock & F. I. M. Craik, (Eds.), *Lifespan cognition: Mechanisms of change* (pp. 162-177). NewYork: Oxford University Press.

Zandi, P. P., Carlson, M. C., Plassman, B. L., Welsh-Bohmer, K. A., Mayer, L. S., Steffens, D. C., Breitner, J. C. (2002). Hormone replacement therapy and incidence of Alzheimer disease in older women: The Cache County study. *JAMA, 288,* 2123-2129. doi:10.1001/jama.288.17.2123.

APPENDICES

APPENDIX A

INFORMED CONSENT FORM

1. This research study will examine factors that are related to words and mood. If you agree to participate, you will be asked to study a series of words presented on a computer screen and then asked to fill out four separate forms.

2. You are free to discontinue your participation at any time without penalty. You may also skip any survey questions that make you feel uncomfortable.

3. Participation in this research study does not guarantee any benefits to you. However, possible benefits include the fact that you may learn something about how research studies are conducted and you may learn something about this area of research (i.e., factors that are related to words and mood).

4. You will be given additional information about the study after your participation is complete.

5. If you agree to participate in the study, it will take about 30 minutes to complete the session.

6. All data from this study will be kept from inappropriate disclosure and will be accessible only to the researchers and their faculty advisor. The researchers are not interested in anyone's individual responses, only the average responses of everyone in the study.

7. The present research is designed to reduce the possibility of any negative experiences as a result of participation. Risks to participants are kept to a minimum.

8. This research study is being conducted by June Newman. The faculty supervisor is Dr. Harold Stanislaw, Professor, Department of Psychology and Child Development, California State University, Stanislaus. If you have questions or concerns about your participation in this study, you may contact the researchers through Dr. Stanislaw at (209) 667-3213. If you need mental health services, you may contact Stanislaus County Behavioral Health and Recovery services at 1-888-376-6246.

9. You may obtain information about the outcome of the study at the end of the academic year by contacting Dr. Stanislaw.

10. If you have any questions about your rights as a research participant, you may contact the Campus Compliance Officer of California State University Stanislaus at IRBadmin@csustan.edu.

11. You will be provided with a blank, unsigned copy of this consent form at the beginning of the study.

12. By signing below, you attest that you are 18 years old or older.

13. By signing below, you are indicating that you have freely consented to participate in this research study.

PARTICIPANT'S SIGNATURE: _____ DATE: _____

APPENDIX B

WORD LISTS

Word List A	*Word List B*
pigment	layman
bishop	summon
felony	discard
comfort	inflict
menace	puzzle
harvest	garment
perfume	empathy
jungle	debate
single	tennis
elevate	torture
warrant	smooth
gossip	pottery
leisure	charity
refugee	balloon
escort	novelty
drawer	master
hunter	settler
sailor	transit
patriot	boycott
canyon	darken

APPENDIX C

SAMPLE STEM COMPLETION TEST

la_ _ _ _

su_ _ _ _

fe_ _ _ _

di_ _ _ _ _

co_ _ _ _ _

in_ _ _ _ _

me_ _ _ _

pu_ _ _ _

ha_ _ _ _ _

wa_ _ _ _ _

sm_ _ _ _

go_ _ _ _

ch_ _ _ _ _

no_ _ _ _ _

hu_ _ _ _

sa_ _ _ _

tr_ _ _ _ _

ca_ _ _ _

da_ _ _ _

ju_ _ _ _

APPENDIX D

DATA COLLECTION FORM

Participant # _____

Age _____ Time since last menses?_____ Surgical/Natural

Glasses/contacts? Yes No Hearing aid? Yes No

Any medications or supplements? Yes No

Which ones? _____

Medical conditions? _____

On HRT? Yes No Previous HRT? Yes ( ) No

Type and dosage? _____Length?_____

Quality of sleep last night: Hrs of sleep? _____

	1	2	3	4	5
	Very poor	Poor	OK	Good	Very good
Physical health?	1	2	3	4	5
Mental health?	1	2	3	4	5

Highest level of education completed?

8↓ 9 10 11 12 12+ AA BA M D

3MMSE: orange, sock, truck

Paragraph A

WMS →→→→→ Start: _____ Finish: _____

LIST **A** or **B** → Start: _____ Finish: _____

Mood scale →→ Start: _____ Finish: _____

Bio/Demo →→→ Start: _____ Finish: _____

IMP →→→→→→Start: _____ Finish: _____

WMS Test →→→ Start: _____ Finish: _____

3MMSE: orange, sock, truck

APPENDIX E

DEBRIEFING SHEET

Thank you for participating in this study! We are interested in understanding the relationship between hormone replacement therapy, mood, and memory among post-menopausal women. By hormone replacement therapy, we mean the use of any combination of hormonal supplementation. One of the more commonly used hormonal supplements is Prempro™. By mood we mean the current emotional state you are experiencing. Mood may be influenced by hormonal states. By memory, we mean the ability to remember words in different ways. Prior research suggests that hormone replacement therapy may have a beneficial effect on verbal memory. In addition, research suggests that we have two different ways to remember words, implicitly and explicitly, and that hormone replacement may affect each type of memory differently. We expect to find similar results in our study. We want to investigate whether there is a difference in how hormonal replacement affects these two types of memory. We predict that hormone replacement therapy will have a much greater impact on implicit memory than it will on explicit memory. In other words, we predict that hormonal replacement therapy helps implicit memory more than explicit memory.

All the information we collected in this study will be kept safe from inappropriate disclosure, and there will be no way of identifying your responses in the data archive. We are not interested in anyone's individual responses; rather, we want to look at the general patterns that emerge when all of the participants' responses are put together. We ask that you do not discuss the nature of the study with others who may later participate in it, as this could affect the validity of our research conclusions.

If you have any questions about the study or would like to learn about the results of the study, you may contact me (June Newman) through my research supervisor, Dr. Harold Stanislaw, at (209) 667-3213. If you have questions about your rights as a research participant, you may contact the Campus Compliance Officer of CSU Stanislaus at IRBadmin@csustan.edu.

If you would like to learn more about this research topic, we suggest the following references:

Sherwin, B. B. (1994). Estrogenic effects on memory in women. *Annals of the New York Academy of Sciences, 743,* 213–230. doi: 10.1111/j.1749-6632.1994.tb55794.x

APPENDIX F

CROSS TABULATION OF RAW IMPLICIT SCORES

HRT Status	Number of correct target words	Number of correct distractor words			
		0	1	2	Total
Current HRT user	0	4	-	-	4
	1	5	-	-	5
	2	6	1	1	8
	3	3	-	-	3
	Total	18	1	1	20
Previous HRT user	0	10	-	-	10
	1	7	1	-	8
	2	-	1	-	1
	3	1	-	-	1
	Total	18	2	0	20
Never used HRT	0	3	2	-	5
	1	10	2	-	12
	2	2	-	-	2
	3	1	-	-	1
	Total	16	4	0	20

Note. The entry in each cell indicates the number of participants achieving the corresponding combination of correct stem completions.