Cognitive Effects of Tamoxifen in Pre-menopausal Women with Breast Cancer
Compared to Healthy Controls

by

Jaime Louise Palmer

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled "Cognitive Effects of Tamoxifen in Pre-menopausal Women with Breast Cancer Compared to Healthy Controls" submitted by Jaime Louise Palmer in partial fulfillment of the requirements for the degree of Master of Science.

Supervisor, Dr. John Mueller, Division of Applied Psychology

Co-supervisor, Dr. Linda E. Carlson, Departments of Psychology and Oncology

Dr. Anne McKeough, Division of Applied Psychology

Dr. Marc Webster, Department of Oncology

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ABSTRACT

Recent research has identified Tamoxifen (TAM) as having potential cognitive effects in women being treated for breast cancer. However, these studies have not controlled for chemotherapy or menopausal status, both of which have their own cognitive effects. The present study compared the cognitive abilities of pre-menopausal TAM users ($N = 20$) who had not received chemotherapy with those of age-matched healthy controls ($N = 20$). TAM users performed significantly lower on verbal fluency ($p = 0.004$), mental rotation ($p = 0.03$), and perceptual speed tasks ($p = 0.01$), and moderate effect sizes were observed for immediate verbal memory ($d = 0.52$) and verbal articulation ($d = 0.49$). The results indicate that TAM may induce widespread cognitive decline that could impact the daily functioning of pre-menopausal users. These effects may be more pronounced than for post-menopausal women, suggesting that special consideration be made prior to prescribing treatment for this population.
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<tr>
<td>ACT</td>
<td>Auditory Consonant Trigrams</td>
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<td>AD</td>
<td>Alzheimer Disease</td>
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<td>BNT</td>
<td>Boston Naming Test</td>
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<td>COWA</td>
<td>Controlled Word Association Test</td>
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<td>CNS</td>
<td>Central Nervous System</td>
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<td>DS</td>
<td>Digit-Symbol subtest</td>
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<td>ER-α</td>
<td>Estrogen Receptor Alpha</td>
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<td>fMRI</td>
<td>Functional Magnetic Resonance Imaging</td>
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<td>HC</td>
<td>Healthy Control</td>
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<td>HRT</td>
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<td>LMI</td>
<td>Logical Memory I</td>
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<td>Logical Memory II</td>
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<td>MRT</td>
<td>Mental Rotation Test</td>
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<td>MWM</td>
<td>Morris Water Maze</td>
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<td>NSABBP</td>
<td>National Surgical Adjuvant Breast and Bowel Project</td>
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<td>OLM</td>
<td>Object Location Memory</td>
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<td>OVX</td>
<td>Ovariectomized</td>
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<td>POMS</td>
<td>Profile of Mood States</td>
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<td>PPB</td>
<td>Purdue Peg Board</td>
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<td>RCF</td>
<td>Rey-Osterrith Complex Figure</td>
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<td>SPSS</td>
<td>Statistical Package for the Social Sciences</td>
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<td>Abbreviation</td>
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<tr>
<td>TAM</td>
<td>Tamoxifen</td>
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<td>WAIS-III</td>
<td>Wechsler Adult Intelligence Test, 3rd Edition</td>
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<td>WMS-III</td>
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CHAPTER ONE

Introduction

Recent increases in the number of individuals who survive cancer and go on to live healthy and productive lives necessitate the investigation of any short or long-term effects of necessary and often intensive cancer treatments. Tamoxifen (TAM) is the most commonly prescribed hormonal drug used for the treatment and prevention of breast cancer (Come, 2006). Although effective in blocking the tumour-fueling properties of estrogen in the breast, little is known about the influence of TAM on other estrogen receptor sites, including the brain. Despite a variety of subjective mood and memory complaints made by women who are using TAM, minimal research has looked to investigate its effects through empirical study.

Most women who are diagnosed with breast cancer are often treated with an adjuvant regime that can include chemotherapy, radiation treatment, and/or surgery in combination with long-term hormonal therapy. It is typical for hormonal therapy to last for five years, extending well-beyond the initial period of intense treatment. Because it is a relatively non-invasive form of treatment without debilitating side-effects, many women continue to participate in normal daily activities such as working full-time, traveling, participating in hobbies, playing sports, and raising families. It is often not problematic for breast cancer survivors to participate in these activities, but changes in cognitive abilities that may be associated with TAM use could alter their task performance, overall behaviour, and quality of life.

Estrogen is a ubiquitous female hormone with a variety of different targets and functions. Since the brain is one of the main target binding sites for estrogen in the body,
it is not surprising that it too would be affected by changes in concentration of the hormone. Estrogen activity has been located in most of the structures associated with learning and memory, including the hypothalamus, amygdala, hippocampus, and prefrontal cortex (see McEwen & Alves, 1999 for a review). In addition, fluctuations in natural estrogen levels throughout the menstrual cycle and during menopause have been implicated in women's performance on tasks of verbal abilities, motor skills, and visuospatial skills (see Kimura, 1999 for a review) as well as working memory (Keenan, Ezzat, Ginsburg, & Moore, 2001). There is also evidence to suggest that lowered estrogen level may be associated with cognitive aging and could play a role in the onset of dementia (see Brinton, 2004 for a review). The use of a drug that blocks the potential influence of estrogen in the brain, therefore, has the potential to seriously alter the cognitive abilities of its users.

There is a limited body of research available to date that has looked at the role of TAM in the cognitive abilities of female breast cancer survivors. In addition to this relative paucity of data in the literature, the studies that are available provide little with which to draw any specific conclusions for application in clinical practice. Because investigators have placed little emphasis on the isolation of confounding factors, the results of TAM studies are often difficult to interpret. Importantly, these factors include the use of tasks that might not be affected by estrogen deprivation, the inclusion of cancer treatment groups that may exhibit cognitive detriment in response to effects other than TAM, and the combination of women with various menopausal statuses, or minimal attention paid to this variable. All of these factors are known to affect cognitive abilities and would serve to confound the results of a study involving estrogen and cognition.
Estrogen has typically been associated with verbal abilities in women; however, only two TAM studies have included a verbal assessment other than verbal memory. One of these studies used a mail-out questionnaire to assess verbal complexity (Paganini-Hill & Clark, 2000), and although the other found changes in performance on a verbal fluency and a verbal learning task, the exact role of TAM in the change was unclear (Castellon, Ganz, Bower, Petersen, Abraham, & Greendale, 2004). Similarly, no studies have included a spatial ability measure other than visual memory. Given the sensitivity of both verbal and spatial abilities to sex differences as well as estrogen fluctuations (Kimura, 1999), it is surprising that these areas of cognition have been neglected in TAM studies. Since they have not been directly investigated, it is difficult to fully determine the extent to which TAM is involved in estrogen-related cognitive abilities.

The inclusion of women who have received chemotherapy with TAM as well as women who had received TAM but not chemotherapy is a serious methodological limitation in some studies (Paganini-Hill & Clark, 2000; Castellon, et al., 2004). Often referred to as ‘chemobrain’ or ‘chemofog’, it is well established now that chemotherapy has its own negative cognitive effects. Some of the areas that have been affected by chemotherapy in cancer patients include language, memory, concentration, attention, and executive functioning (Staat & Segatore, 2005). The results from exclusive breast cancer studies are less clear; however, chemotherapy appears to induce small to moderate declines in overall cognitive functioning in this population when compared to controls (Falleti, Sanfilippo, Maruff, Weih, & Phillips, 2005; Stewart, Bielajew, Collins, Parkinson, & Tomiak, 2006). The possibility of cognitive changes due to chemotherapy
underscore the importance of excluding this treatment group in order to detect any effects associated with TAM alone.

Failing to separate pre- and post-menopausal women is another serious limitation of the previous TAM and cognition research. Changes in memory and cognitive function are often associated with the loss of naturally produced estrogen during menopause (Thompson, 2003). The combination of pre- and post-menopausal women in a cognitive study is therefore problematic in that it is impossible to deconstruct the source of any effects. Similarly, TAM may affect pre- and post-menopausal women differently depending on the level of naturally circulating estrogen present in their bodies. The combination of these two populations would mask any such differences and perhaps produce a null result.

Given the limitations of the previous research regarding the cognitive effects of TAM, the goals of this study were threefold: 1) to utilize an assessment battery that would capture more fully the domains known to be sensitive to either sex differences or estrogen fluctuations in women; 2) to isolate TAM in order to determine its effects exclusively from chemotherapy; and 3) to focus solely on the abilities of pre-menopausal women in order to exclude the potential confounds of the cognitive and memory symptoms commonly associated with menopause.
CHAPTER TWO

Literature Review

As the 'gold standard' of hormonal therapy choices, the majority of women who have been diagnosed with breast cancer will receive TAM in combination with other treatments. Although highly effective in blocking estrogen receptors in the breast tissue, and therefore preventing the growth and spread of tumours, little is known about the biological activity of TAM in the brain. Many women report experiencing changes in their behaviour, mood, and memory as a result of taking TAM; however, little empirical attention has been given to these complaints. It is known that estrogen has widespread effects throughout the central nervous system (CNS) as well as on a variety of cognitive abilities. The following review outlines the research surrounding the effectiveness of TAM as a preventive agent in breast cancer, the neurological and cognitive influences of estrogen, and similarly, the neurological and cognitive influences of TAM. It will conclude with a brief statement of the present study hypotheses.

Breast Cancer

It has been estimated that approximately one in nine women will develop some form of breast cancer throughout their lifetime (National Cancer Institute of Canada (NCIC), 2006). Generally, the earlier the cancer is detected and treated, the better the chances are of it being cured. Developments in the screening, detection, diagnosis, and treatment of breast cancer in recent years have led to an even higher rate of survival for breast cancer patients (NCIC, 2006). Thus, research surrounding the quality of life of survivors post-treatment is becoming increasingly important.
Individuals who have been diagnosed with early stage breast cancer, or that which is limited to the breast and can be easily removed, typically have the best prognosis (Early Breast Cancer Trialists' Collaborative Group, 1998). Surgical removal and radiation therapy are extremely effective (Dollinger, et al., 1997); however, there is always a possibility that microscopic metastatic disease will remain (Early Breast Cancer Trialists' Collaborative Group, 1998). In order to reduce the risk of recurrence and spread hormonal therapy agents, such as TAM, are most often prescribed.

Breast cancer is highly dependent on the concentration of estrogen present in the breast tissue. Because the ducts and lobules within the breast tissue are lined with estrogen receptors, hormonal therapy is useful in modifying the levels of estrogen and resulting in change of the progression of tumour growth and spread (Dollinger, et al., 1994). Many women are tested for the concentration of estrogen receptors present in their breast tumours in order to determine whether hormonal therapy will be effective. Tumours with a high concentration of estrogen receptors are referred to as positive (ER-positive) whereas those with a low or non-existant concentration of receptors are negative (ER-negative). Generally, ER-positive tumours are the target for TAM treatment.

_Tamoxifen as a Treatment for Breast Cancer_

TAM has become the most popular choice for hormonal therapy due to its effectiveness in reducing the recurrence and spread of tumours as well as its relatively low cost (Come, 2006). Although the exact biological mechanism through which TAM operates is not definitively known, many clinical trials have proven the effectiveness of TAM for preventing breast cancer recurrence (Breast Cancer Trials Committee, 1987;

The Anti-tumour Activity of Tamoxifen

Most researchers agree that the anti-tumour activity of TAM occurs once it has successfully bound to estrogen receptors on breast cancer cells. In taking the place of the naturally occurring estrogen, it is likely that TAM modulates the expression of estrogen-regulated genes that would normally induce cell proliferation (Jaiyesimi et al., 1995). TAM is also believed to effect other cell activities, such as preventing the secretion of growth factors and angiogenic factors, and inducing programmed cell death (Osborne, 1998). Ultimately all of these processes result in an imbalance between cell growth and loss, causing regression of breast tumours.

Tamoxifen in Adjuvant Therapy for the Treatment of Early Breast Cancer

Since its introduction in 1977, many randomized clinical trials have obtained favourable results with TAM and the treatment of breast cancer. The benefits of TAM use are most apparent in early low-risk breast cancer cases, where the disease has not yet spread to the lymph nodes (node-negative). A study from the National Surgical Adjuvant Breast and Bowel Project (NSABP), for example, initially reported that there was no survival advantage or disease-free period prolongation associated with adjuvant TAM in patients younger than 49 years (Fisher et al., 1986). However, these patients had disease that had spread to the lymph nodes (node-positive) and had both ER-negative and ER-positive tumours. When only low-risk, node-negative, and ER-positive women were randomly assigned to adjuvant TAM or no TAM groups, the researchers found that there was a significantly prolonged disease-free period for users (Fisher et al., 1989). This
advantage was especially apparent in women younger than 49 years, where the reduction in disease recurrence was 44%.

In a similar trial, the Breast Cancer Trials Committee (1987) compared the duration of disease-free status and the survival rates of women who had either received TAM immediately following mastectomy or had undergone mastectomy but not taken TAM unless a recurrence was detected. The groups contained women who were aged 80 years and below, and either low-risk, node-negative, and pre-menopausal, or low-risk, node-positive, and post-menopausal. The receptor status of the tumours was also considered. When the patient data was examined eight years after the randomization took place, the researchers found that only 24% of the women who had received the TAM had relapsed compared to 38% of the women who had not received the TAM. Although there appeared to be an additional benefit for pre-menopausal women, the node-negative component of their disease may have been a substantial factor in this finding, as they were compared to post-menopausal women who were, in addition, node-positive which indicates a poorer diagnosis. Age was not analyzed as a factor in the effectiveness of the TAM.

In a larger study, The Early Breast Cancer Trialists’ Collaborative Group (1998) analyzed all of the data available from approximately 37,000 women who had participated in 55 randomized clinical trials of TAM conducted world-wide. The participants had either received some form of adjuvant therapy with TAM or some form of adjuvant therapy without TAM. They also analyzed all age groups, estrogen receptor status, and menopausal status. Overall, the researchers found that adjuvant therapy with TAM substantially reduced the rates of recurrence and death associated with breast
cancer. Although there was little benefit found for individuals with ER-negative tumours, those with ER-positive or unrecorded tumours experienced reductions in cancer recurrence by 21% after 1 year of treatment, 29% after 2 years of treatment, and 47% after 5 years of treatment. In addition, the mortality rates of ER-positive women receiving TAM were reduced by 12% after 1 year, 17% after 2 years, and 26% after 5 years. The researchers found that women aged 49 years or younger had experienced a 45% and 32% reduction in the number of relapse and death cases respectively.

Toxicity and Tamoxifen.

Despite its favourable survival and recurrence benefits, the agonist and antagonist effects of TAM throughout the body can result in various negative side effects. In fact, almost all treatment and prevention trials that have involved the drug have also observed an increase in the number of cases of endometrial cancer, presumably due to its agonist effects in this tissue (Early Breast Cancer Trialists' Collaborative Group, 1998; Fisher et al., 1998; Powles et al., 1998). Other somewhat rare, but serious side effects include ocular problems, thromboembolic problems, and stroke in pre-menopausal women (Jaiyesimi et al., 1995; Osborne, 1998). It is not clear whether these problems are associated with the anti-estrogen properties of TAM.

In addition to the physical side effects, many women using TAM have reported experiencing menopause-like symptoms that could be associated with an overall reduction in estrogen activity (Anthony, Williams, & Dunn, 2001). Gallicchio et al. (2004) found that many women taking TAM reported symptoms of hot flashes (67%), vaginal dryness (24%), insomnia (24%), and vaginal discharge problems (18%). Similarly, Rohatgi, Blau, and Lower (2002) found that at least 36% of women taking
TAM reported symptoms including hot flashes, vaginal discharge and dryness problems, and weight gain. It is important to note that pre-menopausal women more often experienced the undesirable side effects associated with TAM (Jaiyesimi et al., 1995; Osborne, 1998), presumably due to the precipitous changes in estrogen levels. This makes sense given that they were formerly producing high levels of estrogens and with the use of TAM were thrown quickly into premature menopause. In fact, women aged 35-49 showed the greatest increase in frequency of hot flashes, and vaginal discharge problems than other age groups in the NSABBP study (Day et al., 1999).

Additional symptoms that could be associated with the anti-estrogen effects of TAM, such as changes in behaviour, mood, and memory, have also been reported. For example, Rohatgi et al. (2002) found that 35% of TAM users reported a decrease in sexual desire, whereas 31% had experienced general mood changes. Gallicchio et al. (2004) observed similar symptoms; they found that 15% of women surveyed reported symptoms of depression and that 11% had experienced memory loss after taking TAM.

There is also some evidence to suggest that these symptoms have been under-reported. Arnold, et al. (2001) found that women with highly stressful lives tend to under-attribute side-effects to TAM use (Arnold et al., 2001). In addition, 41% of the total number of participants who had discontinued TAM in the NSABBP prevention study cited non-medical reasons (Day et al., 1999), which suggests that women who had experienced the most severe behavioural changes may have stopped treatment early on. Although this study included a mental health measure, upon which they observed no differences between treatment groups, the measure is very brief and it is therefore unlikely that any specific cognitive deficits would have been captured by using it. It is
more likely that many women who have experienced significant cognitive effects while using TAM would not have been included in the studies of its detrimental psychological influence because of their unwillingness to continue treatment.

Both the biological and cognitive side-effects that have been associated with TAM suggest that either the antagonist or agonist activity of the drug interfere with typical bodily functions dependent on estrogen. Compared to the physical side effects of TAM, however, the cognitive effects of TAM may be more complex. As we know relatively little about how the brain works, there could be a variety of mechanisms and regions through which TAM could interfere with behaviour, mood, and memory. Although the brain is a target site for estrogen in the body, there is little known about the function of TAM in this organ (Birge, McEwen, & Wise, 2001).

_Estrogen in the Central Nervous System_

It has become increasingly clear in recent years that estrogen has an important influence upon the structure and function of the CNS. There is now an abundance of evidence to show that estrogen is directly involved in the regulation of hippocampal synapses, cellular signaling through both genomic and non-genomic mechanisms (for a review, see Woolley, 1999), and the regulation of neuronal activity patterns (for a review, see van Amelsvoort, Compton, & Murphy, 2001). Most of this evidence has been obtained through animal studies; however, recent human research has surfaced through the utilization of brain imaging techniques. Although current knowledge is not exact, the role of estrogen in the CNS appears to have direct implications for cognitive function.
Important Findings from Animal Research

Woolley and McEwen (1992) were first to report that estrogen could regulate the density of synapses in the CA1 region of the rat hippocampus. The researchers found that ovariecomized rats that were treated with estradiol exhibited a 38% increase in the density of dendritic spines on the CA1 pyramidal cells compared to those treated with a control substance. Similarly, they found that when adult rats were in transition from proestrous (high estrogen) to estrous (low estrogen) during the naturally occurring estrous cycle, there was a 32% decrease in the number of dendritic spines observed in the CA1. More recently, Leranth, Shanbrough, and Redmond (2002) observed a 40% increase in the volume of dendritic spines in the hippocampi of adult primates treated with estradiol compared to those who were not treated. Given that the hippocampus is generally accepted as a crucial structure for cognitive function (McEwen & Alves, 1999), the results of these studies suggest a potentially important role for estrogen in these functions.

The complexity of estrogen’s involvement in cellular signaling processes was increasingly recognized when it was discovered that there are two different estrogen receptors (for a review, see McEwen & Alves, 1999). Although the exact functions of each receptor are unknown, there is a growing body of evidence to suggest that estrogen receptor alpha (ER-α) and estrogen receptor beta (ER-β) are differentially expressed throughout the CNS. Blurton-Jones, Roberts, and Tuszynski (1999) observed a small, scattered number of ER-α receptors in the hippocampal region and a large number distributed in the amygdala and hypothalamus of adult primate brains. Estrogen receptor β mRNA, on the other hand, was seen at high levels throughout the hippocampus, dentate
gyrus, and subiculum (Gundlah et al., 2000). Although this research is preliminary, the differential distribution of the two receptor sub-types suggests that each may have a different role in brain function. Whether TAM binds to one receptor, the other, or both requires further investigation; however, it can be speculated that depending on where TAM binds, it could have varying cognitive effects.

**Human Histological and Brain Imaging Studies**

Further evidence for the complexity of the role of estrogen in the control of cognitive functions was found in a recent study that looked at the brains of 10 deceased humans. Examining estrogen receptor mRNA, Oesterlund, Gustaffson, Keller, and Hurd (2000) found distinct distribution patterns for ER-α and ER-β. Similar to studies with primate tissue, the distribution of ER-α was highest in the amygdala and hypothalamus. In contrast, the researchers found that although expression was relatively low throughout the brain, ER-β was distributed in the hippocampus, claustrum, thalamus, and cerebral cortex. The distribution patterns of the two receptors may suggest different functions, each having a specific role in the modulation of neurological processes presumably associated with cognitive behaviours. The effects of each require further investigation, however, although speculative, it appears that ER-α may be involved in autonomic processes such as hormonal regulation, reflexes, and the modulation of emotions, whereas ER-β may be involved in higher order cognitive functions such as learning, memory, and executive functioning.

Circulating estrogen has also been implicated in the regulation of neuronal activity in the prefrontal cortex. Using positron emission tomography (PET) scanning techniques, Berman et al. (1997) examined the cerebral blood flow of 11 healthy females
treated with lupron, a drug that completely blocks the secretion of estrogen and progesterone. The women were asked to perform a task known to be reliant on the prefrontal cortex, but surprisingly, when treated with lupron, there was no activity observed in this area. The fact that pre-lupron activity was restored in the prefrontal cortex when estrogen or progesterone was replaced suggests that the cognitive functions dependent on this structure may be directly influenced by hormones.

Estrogen may also be involved in protection against age-related decline in activity in areas important for verbal and visual memory. Using PET technology, Maki and Resnick (2000) compared brain activity of 12 hormone replacement therapy (HRT) users with 16 non-users in order to determine the effect of the estrogen replacement in women who had been users for over two years. Overall, the researchers found that HRT users exhibited increased cerebral blood flow over time. Specific increases were observed in a variety of areas, including the hippocampus, para-hippocampal gyrus, and temporal lobe. In addition, the increased activity in these areas correlated with the higher performance of HRT users on tasks of verbal and prospective memory. Thus, the increased estrogen available in the brains of the HRT users appeared to have increased the activity in areas important for memory functions.

A similar role for estrogen in the regulation of neuronal activity was observed by Dietrich et al. (2001) using functional magnetic resonance imaging (fMRI). In their study, the researchers examined 6 females at two distinct points in the menstrual cycle. They found no difference between the patterns of regional activation observed in the brains of the females at either the low or high estrogen time points. Interestingly, however, they observed a significant decrease in the strength of the activation signals
observed at the low estrogen phase of the cycle. Although this difference was more substantial during tasks that involved mental rotation and verbal fluency, slight alterations were also observed during a fine motor task. Thus, estrogen may be more involved in the regulation of the strength of neurological activation patterns, at least for the tasks administered in this study, than the differential activation of brain structures.

Estrogen seems to have a profound and complex effect on the regulation of neurological processes presumed to be involved in cognition. The differential distribution of ER-α and ER-β in the animal and human brain suggests that these receptors are responsible for the regulation of different activities, although the nature of this difference is yet to be determined. Brain imaging studies, along with animal studies of synapse regulation seem to suggest that hormonal activity may have more to do with the speed and strength of neural transmission rather than localization of it. Fluctuations in the amount of estrogen available for neurological processes, therefore, will likely have important effects on cognition.

**Estrogen and Cognition**

Much research has shown that estrogen has an important influence on the performance of certain cognitive tasks, especially those involving fine motor skills, working memory, verbal ability, and visuo-spatial ability. Estrogen has been implicated as affecting cognition in older, post-menopausal women utilizing HRT, as well as in younger, pre-menopausal women throughout their menstrual cycles. Overall, the results indicate that there is an optimum level of estrogen required for average functioning related to each task, and that changes in this level manifest in altered performance scores.
Fine motor skills. The fine motor ability of women has been most often tested using the Purdue Peg Board task, which involves the placement of different sized pegs in appropriate holes along a wooden board within a certain amount of time (Kimura, 1999). Females have been consistently shown to have an advantage over males on the efficient and accurate performance of this task, and this advantage has been shown to depend upon estrogen level (Kimura & Hampson, 1994). Using a counter-balanced, within-subjects design, the researchers found that 45 college females performed better on the Purdue Peg Board task during the pre-ovulatory phase of their menstrual cycles, when estrogen levels were presumed to be highest, than they did at the late menstrual phase when estrogen levels were presumed to be lowest.

In a cross-sectional study, Kimura (1995) found that post-menopausal women, aged over 50 years, who were taking HRT ($n = 21$) performed better on a motor sequencing task similar to the Purdue Peg Board than those who were not taking HRT ($n = 33$). Although it is important to note that because women are not usually randomly assigned to take HRT, there may be differences inherent in those that choose to take it compared to those that do not. If these two groups were different to begin with, it would be difficult to determine whether the cognitive differences obtained were due to estrogen or to other cognitive factors. In order to control for this, the authors in this study asked for the reasons that women gave for taking HRT. They found that the majority of reasons were unrelated to intelligence or increased knowledge about the potential cognitive benefits of HRT, rather they surrounded coaxing or encouragement from their friends, family, and doctors. The women were also similar in their level of education, indicating that the cognitive differences observed in this study may be attributed to the HRT.
Working memory. At least two recent studies have found that HRT has a positive effect on the performance of working memory tasks that are dependent on the pre-frontal cortex. Keenan, Ezzat, Ginsburg, and Moore (2001) compared the performance of women who were currently taking HRT ($M_{\text{age}} = 51.6$ years) with that of women who were not ($M_{\text{age}} = 54.3$ years) on the N-back test, which requires participants to repeat increasingly longer strings of numbers heard on tape back to an administrator. Interestingly, as the complexity of the task increased, HRT users performed significantly better than non-users. It is important to consider, however, that the sample size in this study was small ($N = 19$) and the researchers did not assess the mood states of the participants at the time of testing. It is possible that these results could be due to chance or that individuals in the no HRT group were suffering some distress that interfered with their performance.

In a similar study, however, Duff and Hampson (2000) used a cross-sectional design to examine the abilities of three groups of post-menopausal women with an average age of 55 on two working memory tasks. The first group was taking an estrogen-only HRT ($n = 38$), the second group was taking an estrogen-progestin HRT ($n = 23$), and the third group was not taking any replacements ($n = 35$). The spatial task required the participants to find matching pairs of coloured dots in a 4X5 array of overturned index cards. The participants were only allowed to reveal two cards at a time. The verbal task was called digit ordering, and it required the participants to say aloud the numbers from one to ten in a random order without forgetting or repeating any. Interestingly, the researchers found that the women who were taking either the estrogen-only or the estrogen-progestin HRT performed significantly better on both working memory tasks.
than individuals who were not taking anything. Although similar consideration regarding the cognitive ability of participants prior to the initiation of HRT applies to this study, the results, in combination with the results obtained by Keenan, et al. (2001) suggested that estrogen may help to mediate women’s performance on working memory tasks dependent on the pre-frontal cortex, especially those of increasing complexity.

*Verbal abilities.* Many studies have identified a beneficial effect of estrogen on verbal articulation, fluency, and memory. Verbal articulation involves the ability to name and articulate words, numbers, or objects. Hampson (1990) used a counter-balanced, within-subjects design in order to identify the role of estrogen in performance of a verbal articulation task. Interestingly, she found that young females ($n = 45$) with an average age of 23 years performed significantly better on tasks including counting to 50, naming colours, and repeating syllables when in the pre-ovulatory phase (high estrogen) rather than the menstrual phase (low estrogen) of the menstrual cycle. Despite the fact that the authors were unable to control for confounds such as mood at the time of testing, the fact that individual participants were tested twice, in a counterbalanced order, and the difference between their two performance scores was used for analysis, suggests that estrogen mediates verbal articulation skills in young, pre-menopausal women.

Hampson (1990) also tested participants on two verbal fluency tasks. In the first task, the women were asked to name as many words as they could that began with the letter ‘d’. In the second task, they were asked to write as many four-word sentences, with each word beginning with a specific letter, as quickly as possible in four minutes. Similar to the results of the verbal articulation tasks, the author found that the women performed significantly better on the verbal fluency tasks during the pre-ovulatory phase rather than
the mid-luteal phase of their menstrual cycles. Presumably, high estrogen during the pre-ovulatory phase was associated with the better performance on these tasks. Again, the results of this study provide additional evidence to support the role of estrogen in promoting verbal abilities in women.

The performance of post-menopausal women on tasks of verbal articulation and fluency was investigated in a cross-sectional study by Kimura (1995). To measure verbal articulation, the author asked women aged over 50 years to recite a series of tongue-twisters. Verbal fluency was measured through a naming task in which participants were presented with a book of different colours to name, and a sentence task where participants were asked to write sentences with constraints placed upon the beginning letters of each word. In line with previous studies, the researcher found that those women taking HRT (n = 21) performed better than those who were not (n = 33) on both the verbal articulation and verbal fluency tasks. Although confounding is possible, it is unlikely given that the two participant groups were well matched in terms of age, level of education, and scores obtained on a vocabulary task.

Perhaps the most striking effects of estrogen on verbal abilities are observed in tests that involve verbal recall (for a review, see Sherwin, 1999). Most studies have used tests of paragraph recall in which participants are asked to verbally recall words or information from a dictated paragraph either immediately or after a short delay. Whether or not this task is sensitive to natural fluctuations in estrogen is unclear. Although Phillips and Sherwin (1992b) did not observe any differences on this task amongst participants in the high and low estrogen phases of their menstrual cycles, Drake et al. (2000) found that
levels of bio-available estrogen in the blood were significantly positively correlated with delayed recall performance in post-menopausal women.

Hormone replacement therapy, on the other hand, has been shown to elevate the performance of women on verbal recall tasks. Phillips and Sherwin (1992a) administered the tasks to women before they underwent surgery to remove either their ovaries or their uteri, and then again two months after they had been taking either HRT or a placebo. When scores were compared, researchers found that estrogen users' scores improved significantly from baseline, whereas the non-users did not. In addition, the performance of the women who had received a placebo declined significantly from baseline on tasks of immediate and delayed recall of associated word pairs.

Sherwin and Tulandi (1996) obtained similar results when they examined the cognitive performance of women who were preparing for the surgical removal of uterine myomas. The relatively young women were first treated with a gonadotropin-releasing hormone agonist (GnRH-a), which decreases the production of estrogen, to effect regression of tumours. They were then given either an estrogen "add-back" therapy or a placebo, and subsequently given surgery. As expected, researchers found that scores of the participants on immediate and delayed paragraph recall tests declined significantly after twelve weeks of GnRH-a treatment and concomitant estrogen withdrawal. When tested again eight weeks later, however, the performance of the participants who had received estrogen replacement had improved to baseline levels, whereas the performance of the placebo group remained low. These effects were significant, given the tightly controlled experimental design of the study, indicating a specific role for estrogen in the maintenance of verbal memory ability.
Spatial abilities. Performance on tasks of certain spatial abilities has been shown to be affected by estrogen. Mental rotation, or the ability to mentally rotate three-dimensional objects in mind, has been consistently shown to exhibit a male advantage (Kimura, 1999). Interestingly, however, the highest female performance on such tasks has also been associated with an optimum level of estrogen. Both Hampson (1990) and Silverman and Phillips (1993) found that younger, pre-menopausal females performed best on spatial tasks when they were in the menstrual phase of their menstrual cycles, when estrogen levels are moderate. In contrast, there is some evidence to suggest that treatment with HRT in post-menopausal women enhances performance on spatial rotation tasks when compared to no treatment (Kimura, 1995). Thus, it seems that some estrogen is better than either no estrogen or high estrogen for the performance of mental rotation tasks.

It should be noted that at least one study has observed detrimental cognitive effects to HRT. Using an adapted form of a brief cognitive measure typically used to screen for dementia in elderly patients, the Women’s Health Initiative Memory Study tested over 2800 post-menopausal women who were randomized to take either estrogen replacement or placebo. In short, researchers found that women aged 65 years and older who had taken the estrogen therapy scored significantly lower on the cognitive measure than those who had taken placebo. This result suggests that the therapy ultimately leads to cognitive decline with age, however, the brevity of the measure used makes it difficult to conclude this. In addition, all of the women in the study had undergone hysterectomy, and the women in the estrogen therapy group were less educated and reported lower household income levels than those in the placebo group. All of these factors call the
result into question; it is more likely that estrogen has a positive effect on cognitive abilities, especially when specifically measured.

In sum, high levels of estrogen appear to be associated with enhanced performance on a variety of tasks, including those of motor and articulatory skills, working memory, and verbal memory. Lower estrogen levels, on the other hand, may be associated with optimum performance on other tasks, such as mental rotation. The role of estrogen antagonist drugs, such as TAM, therefore, may have widespread and differential effects depending on the domain studied.

*_Tamoxifen in the Central Nervous System_*

There is a growing body of evidence to suggest that TAM binds in a regionally-specific pattern consistent with the proportion of ER-α and ER-β receptors present in certain regions of the CNS. Pareto, Alvarado, Hanrahan, and Biegon (2004) found that the binding ability of the ER-ligands, \[^{18}F\]FES and \[^{125}I\]MIE\_2 were reduced in the cortical amygdala (84%), anterior paraventricular thalamus (74%), central grey (71%), frontal cortex (55%), and hypothalamus (47%) of OVX, TAM treated rats. In other words, because the rats were not producing estrogen due to their surgery, their estrogen receptors should not have been occupied. Because the ligands could not bind to the receptors, it is likely that they were already occupied by TAM. It is clear that there is blockage of estrogen binding in these areas due to TAM; however, the study did not identify whether the binding of TAM was agonist or antagonist, or which of the ER subtypes were occupied in each area.

There is evidence to suggest that TAM acts as an agonist in the hippocampus. Ciriza, Carrero, Azcoitia, Lundeen, and Garcia-Segura (2004) found that TAM
administration to the pyramidal region of the hippocampus could block the excitotoxic effects of kainic acid on the CA1 and CA3 cells. In addition, Silva, Mello, Freymuller, Haidar, and Baracat (2000) found that TAM induced a 47% increase in synaptic density of the CA1 pyramidal cells. These studies argue that TAM may have an agonist effect on the hippocampus. Given the fact that both ER-α and ER-β have been identified in this structure (Shughrue, Scrimo, & Merchenthaler, 2000) however, it is difficult to discern which of the two receptor subtypes was responsible for this effect.

Barkhem, Carlsson, Nilsson, Enmark, Gustaffson, and Nilsson (1998) found that ER-α and ER-β responded differently to TAM in vitro. Using cloned reporter cells that possessed each receptor type, researchers found that TAM had low agonist activity when bound to the ER-α, but only antagonist activity when bound to the ER-β. In addition, Rissman, Heck, Leonard, Shupnik, and Gustaffson (2002) found that not only were ER-β knock-out mice impaired in performance of the Morris Water Maze (MWM), the impairment was not alleviated with estrogen replacement. The antagonist activity of TAM in humans, therefore, may affect cognition that is dependent on regions of the CNS that have high densities of ER-β, such as the hippocampus and the cerebral cortex.

Recent evidence from human brain imaging studies seem to confirm this hypothesis. Using PET technology, Eberling, Wu, Tong-Turnbeaugh, and Jagust (2004) examined the brains of ten women who were taking TAM as a treatment for breast cancer. Interestingly, the researchers found that the women had widespread hypometabolism of glucose similar to that of post-menopausal women who had not taken HRT. The loss of estrogen that would presumably be related to both conditions resulted in an observable lack of activity bilaterally throughout the superior and inferior frontal...
cortices, and into the parietal cortex of the TAM users. Additionally, the researchers observed a striking trend toward reduced tissue volume in the hippocampus of TAM users. It is possible, therefore, that observable negative cognitive effects may correlate with these changes.

*Tamoxifen and Cognition*

There are very few studies that have evaluated the effects of TAM on cognition, and the studies that are available have many limitations and potential confounding variables which make their results questionable. For example, it is often difficult to isolate TAM as the only therapy being used to treat breast cancer. Commonly referred to as ‘chemo-brain’, research has shown that chemotherapy can have its own detrimental effects on cognitive abilities, therefore confounding the results of many of these studies. In a recent meta-analysis, Stewart, Bielajew, Collins, Parkinson, and Tomiak (2006) found that chemotherapy treatment was associated with declines of small to moderate effect size in eight cognitive domains. These included working, short-term, and long-term memory, processing speed, language, spatial abilities, and motor abilities. As most of these studies did not isolate TAM, chemotherapy, or menopausal status, further study is required.

In their analysis of six studies, Falleti, Sanfilippo, Maruff, Weih, and Phillips (2005) found similar cognitive declines associated with chemotherapy. Interestingly, however, they also found that greater cognitive decline was associated with study participants using TAM in combination with chemotherapy versus chemotherapy alone. Lower scores on cognitive tasks were also associated with younger patient age, suggesting that menopausal status may play a role in the extent to which cognitive
abilities are affected. These trends indicate that in addition to a negative effect of TAM alone, it may have a more detrimental influence on cognitive abilities when it is taken by pre-menopausal users. Importantly, however, it is still impossible to determine whether chemotherapy, TAM, or both treatments resulted in the cognitive changes observed in these studies.

van Dam et al. (1998) used a cross-sectional study to compare the task performance of three groups of women. The first group had undergone a high dose of chemotherapy with TAM \((n = 34, M_{age} = 45.5 \text{ years})\), the second group had undergone a standard dose of chemotherapy with TAM \((n = 36, M_{age} = 48.1 \text{ years})\), and the third group were healthy controls who had not received any therapy \((n = 34, M_{age} = 46.1 \text{ years})\). The researchers found that women in the high-dose group scored significantly lower than healthy controls, but not significantly lower than the standard chemotherapy group, on tasks of motor function, visual memory, information processing, and short-term memory. The results suggest that there may be negative effects of TAM on cognition; however, there is no way to discern whether any or which effects were due to the TAM versus the dose of chemotherapy. Furthermore, there was no attention given to the menopausal status of the participants in this study. Given the probability of differences in the cognitive performance of pre- and post-menopausal women, the combination of their scores for analysis is a serious limitation.

In a more recent study, Castellon et al. (2004) used a cross-sectional design to compare the performance of individuals who had undergone chemotherapy alone \((n = 17, M_{age} = 48.3 \text{ years})\), chemotherapy plus TAM \((n = 36, M_{age} = 46.8 \text{ years})\), and healthy controls \((n = 19, M_{age} = 49.2 \text{ years})\). The researchers found that women who had
received adjuvant therapy with TAM scored significantly lower than the healthy control women, but not significantly lower than the chemotherapy only group, on tasks of visual memory, verbal fluency, and visuospatial ability. Again, however, because the adjuvant TAM group did not differ significantly from the chemotherapy only group, the exact role of TAM in these effects cannot be isolated. The researchers also did not state explicitly whether their participants were pre-, peri-, or post-menopausal. Because they could have been either, the results are further confounded. The loss of estrogen associated with normal aging cannot be separated from that of the potential antagonist effects of TAM.

In contrast, Bender et al. (2006) used a between-subjects, repeated measures design to compare the performance of pre- and peri-menopausal women with an average age of 42.57 years. There were three groups of participants: (a) women who had received chemotherapy only \( (n = 19) \), (b) women who had received chemotherapy and TAM \( (n = 15) \), or (c) women who had been diagnosed with breast cancer but had not received chemotherapy or TAM. Each group was tested at three different time points. They were tested immediately after surgery, one week after the completion of chemotherapy, if applicable, and one year later. The researchers found that the chemotherapy and TAM group exhibited significant deficits in verbal working memory and visual memory when compared to the no treatment group at the third time point. The chemotherapy only group also exhibited deficits in verbal working memory across time, whereas the control group performance tended to increase over time. The results of this study suggest a negative effect of TAM on visual memory scores, however, there are several limitations that should be noted. First, the lack of a TAM only group makes it impossible to determine whether the cognitive deficiencies observed in this study were due to chemotherapy,
TAM, or the combination of both. Second, each treatment group was comprised of patients that had a different stage of cancer. For example, the chemotherapy and combined chemotherapy with TAM groups included patients with both Stage I or II cancers, whereas the no treatment group was comprised of patients diagnosed with Stage 0 or ductal carcinomas in situ. It is impossible to know whether the disease severity difference between groups may have had an effect on the results. Lastly, on a self-report questionnaire of symptoms, the TAM group reported significantly more memory loss than either of the other treatment groups. Because there was no clear difference observed in the abilities of the chemotherapy only and chemotherapy plus TAM groups in this study, the tests used in this study may not have accurately encapsulated all of the cognitive effects of TAM use as observed by the users themselves.

Subjective complaints reported by post-menopausal TAM users were also found by Paganini-Hill and Clark (2000). In their cross-sectional comparison of TAM users \( n = 710 \) and breast cancer survivors who had never used TAM \( n = 453 \), participants returned a mail-out questionnaire that included some simple cognitive tasks as well as questions about their experiences. They found that TAM users did not differ significantly from the non-TAM users on either a box-drawing task, or a clock-drawing task. However, TAM users did exhibit significant deficits in a verbal complexity task. The researchers also found that TAM users reported significantly more subjective complaints of memory loss, which may indicate a more pronounced role for the drug in cognition than was captured by the tasks in this study. It is also important to note that the participants completed the cognitive tasks at home by way of a mail-out questionnaire. It is difficult, therefore, to determine whether this is an accurate estimate of the
participants' functioning, as they could have taken as much time or as many tries as necessary. Furthermore, anyone could have responded or helped with completing the tasks. The researchers also failed to distinguish whether respondents were pre- or post-menopausal or had received other cancer treatments, which likely introduced confounds to the results.

Using a more comprehensive test battery, Shilling, Jenkins, Fallowfield, and Howell (2003) tested the cognitive abilities of women who were taking either TAM or an alternative drug, Anastrozole, or a combination of both for the adjuvant treatment of breast cancer compared to a healthy control group. Anastrozole is not an anti-estrogen, but an aromatase inhibitor, which works to inhibit the conversion of androgens to estrogen rather than to block estrogen receptors (Come, 2006). Although the design was cross-sectional, all study participants were post-menopausal and the groups were matched on age, education level, and estimated IQ. Interestingly, the researchers found that when compared with matched healthy controls \((n = 35)\), the participants in the drug group \((n = 94)\) exhibited significantly lower scores on tests of immediate verbal recall and perceptual speed. It is important to note that the researchers were blind to which treatment each participant had taken. When the results were split into three treatment groups (A, B, and C, each corresponding to a different treatment regime), however, it was evident that the treatment received in one group affected processing speed and the other verbal memory. Unfortunately it will be impossible to determine the specific role of each treatment until the treatment arms are unveiled, and this study will not provide any insight into the effects of either drug in pre-menopausal women who are still producing circulating estrogen.
Summary

Although TAM has agonist as well as antagonist activity in the brain, it is predominantly anti-estrogenic in the breast tissue. It has been shown to be highly effective for the treatment and prevention of estrogen receptor positive breast cancer due to its activity in the breast, and as a result, is frequently prescribed. It is important for both patients and professionals to be informed of potential side effects of the drug whether physical or cognitive. Estrogen has a ubiquitous effect within the body, including the CNS, which may be observable in various aspects of cognitive function. The use of TAM appears to influence this system, but given the existing confounds in the literature, more stringent studies are required to disentangle the effects of menopausal status, other treatments, and the specific cognitive abilities affected.

The Present Study

In order to help inform medical and psychological practitioners as well as patients of the potential symptoms that may be associated with hormonal therapy in breast cancer, the purpose of this study was to augment to and improve upon the current literature and elucidate the effects of TAM.

Study Objectives

There were three main objectives of this study, as described in the previous section:

1. To ensure the exclusive assessment of the cognitive abilities of pre-menopausal women using TAM.
2. To ensure the isolation of TAM from chemotherapy in order to further clarify its role in the cognitive abilities of the study participants.
3. To clarify the specific cognitive domains that may be influenced by TAM through a comprehensive and relevant assessment battery.

**Study Hypotheses**

Using a cross-sectional design, the following hypotheses were tested in this study:

1. TAM users will exhibit lower performance on an immediate verbal memory task than non-users:  
   \[ H_0: \mu_{(TAM)} = \mu_{(No\ TAM)} \quad H_a: \mu_{(TAM)} < \mu_{(No\ TAM)} \]

2. TAM users will exhibit lower performance on a delayed verbal memory task than non-users:  
   \[ H_0: \mu_{(TAM)} = \mu_{(No\ TAM)} \quad H_a: \mu_{(TAM)} < \mu_{(No\ TAM)} \]

3. TAM users will exhibit lower performance on a verbal fluency task than non-users:  
   \[ H_0: \mu_{(TAM)} = \mu_{(No\ TAM)} \quad H_a: \mu_{(TAM)} < \mu_{(No\ TAM)} \]

4. TAM users will exhibit lower performance on a verbal articulation task than non-users:  
   \[ H_0: \mu_{(TAM)} = \mu_{(No\ TAM)} \quad H_a: \mu_{(TAM)} < \mu_{(No\ TAM)} \]

5. TAM users will exhibit lower performance on a spatial memory task than non-users:  
   \[ H_0: \mu_{(TAM)} = \mu_{(No\ TAM)} \quad H_a: \mu_{(TAM)} < \mu_{(No\ TAM)} \]

6. TAM users will exhibit lower performance on a working memory task than non-users:  
   \[ H_0: \mu_{(TAM)} = \mu_{(No\ TAM)} \quad H_a: \mu_{(TAM)} < \mu_{(No\ TAM)} \]

7. TAM users will exhibit lower performance on an immediate visual memory task than non-users:  
   \[ H_0: \mu_{(TAM)} = \mu_{(No\ TAM)} \quad H_a: \mu_{(TAM)} < \mu_{(No\ TAM)} \]

8. TAM users will exhibit lower performance on a delayed visual memory task than non-users:  
   \[ H_0: \mu_{(TAM)} = \mu_{(No\ TAM)} \quad H_a: \mu_{(TAM)} < \mu_{(No\ TAM)} \]

9. TAM users will exhibit lower performance on a fine motor skills task than non-users:  
   \[ H_0: \mu_{(TAM)} = \mu_{(No\ TAM)} \quad H_a: \mu_{(TAM)} < \mu_{(No\ TAM)} \]
10. TAM users will exhibit lower performance on a perceptual speed task than non-users:

\[ H_0: \mu_{(TAM)} = \mu_{(No\ TAM)} \quad H_a: \mu_{(TAM)} < \mu_{(No\ TAM)} \]

11. TAM users will exhibit higher performance on a mental rotation task than non-users:

\[ H_0: \mu_{(TAM)} = \mu_{(No\ TAM)} \quad H_a: \mu_{(TAM)} > \mu_{(No\ TAM)} \]
CHAPTER THREE

Method

Participants

In order to isolate the effects of TAM on the cognitive abilities of women, this study took advantage of an already existing population of TAM users for comparison with a healthy control population.

Eligibility

The following inclusion criterion were used to determine eligibility for participation in the study: (a) Female; (b) Aged 18 years or older; (c) Use of TAM for the adjuvant treatment of early, low-risk, ER-positive breast cancer for at least two weeks, OR No history of breast cancer or TAM use; (d) Completion of any radiation therapy or surgery for at least one month, if applicable; (e) Pre-menopausal status, defined by self-reported menstruation within the past month.

In contrast, participants who met any of the following criterion were excluded from the study: (a) Current or past history of chemotherapy; (b) Diagnosis of receptor-negative or unknown classification of tumour(s), if applicable; (c) Diagnosis of node-positive disease, if applicable; (d) Current use of psychotropic drugs that affect cognition, such as benzodiazepines and beta-blockers. Stabilized use of anti-depressants was considered on an individual basis; (e) Current use of drugs that manipulate hormone levels (i.e. birth control pills); (f) Previous hysterectomy or ovariectomy; (g) Existing DSM-IV Axis 1 mood, anxiety, or depressive disorder by self-report.
Recruitment

A total of 40 participants, 20 in the TAM and healthy control (HC) groups respectively, completed the study. The participants in both groups were age-matched in order to avoid confounding effects due to cognitive change often associated with aging.

Tamoxifen group (TAM). Using a pre-existing database of local breast cancer patients, the leader of the Breast Tumour Group at the Tom Baker Cancer Centre (TBCC), Calgary, AB, screened patients for eligibility in this study. At this stage of recruitment, screening criteria were based on disease characteristics and menopausal status. Only pre-menopausal women who had received either radiation therapy or surgery in combination with TAM were selected. The contact information of these individuals was then forwarded to the researcher for further recruitment.

A total of 59 eligible TAM group participants were identified by the patient review and subsequently contacted by the researcher for further recruitment. Of those 59, 20 (34%) participated in the study. Of the 39 who did not participate, 18 were not interested, 11 could not be contacted due to factors such as incorrect or disconnected phone numbers, 4 were of post-menopausal status, 3 were not fluent in English, 2 were no longer taking TAM, and 1 did not attend the appointment.

Healthy control group (HC). Participants for the HC group were recruited from the community using a variety of advertising methods. Posters (Appendix B) were placed throughout the buildings of the university including the Faculty of Education, the women's locker room of the university gymnasium, and the Department of Psychology. An electronic advertisement was also placed on the University of Calgary Health Sciences recruitment website (Appendix C). In order to reach women outside of the
university, an advertisement (Appendix D) was placed in a local women's magazine as well as a freely accessed community newspaper. Women were also encouraged to contact the researcher with regard to the study following word of mouth referral by other participants.

A total of 61 women responded to the study advertisements. Although 36 (59%) of those 61 participants completed the test battery, 16 were excluded due to criteria for age-matching with the TAM group. Of the remaining 25 respondents, 9 could not find a convenient time to meet with the researcher, 7 were using hormonal birth control or related drugs, 4 did not attend the appointment, 2 were of post-menopausal status, 1 was not fluent in English, 1 had a history of clinical depression, and 1 wanted monetary remuneration. Twenty (33%) of the initial 61 respondents were ultimately included in the study for participation in the comparison group.

**Demographics**

All participants were females between the ages of 40 and 50 years old. Most were Caucasian (90%) and had obtained at least an undergraduate degree (55%). In addition, most were married or living in a married-like relationship (73%). Most of the participants were employed in full time positions (58%) and reported a combined household income of at least $60,000 per year (68%).

**Procedure**

During recruitment, the researcher contacted all individuals by telephone. At that time, the details of the study were explained and they were asked if they were interested in participating. Those who were not interested were thanked for their time and their reason for lack of participation was noted. Those who were interested were confirmed for
eligibility by the researcher using a series of questions included in the telephone pre-screening protocol created for this study (Appendix E). For the purpose of recruitment records, the researcher retained the contact information of all uninterested and excluded participants, as well as their reasons for not being included in the study.

All participants included in the study met once with the researcher at the TBCC Holy Cross Site, Calgary, AB, or the University of Calgary, Calgary, AB, for testing. The session took place in a quiet testing room or private office and lasted no longer than 1.5 hours. On two occasions, the researcher traveled to the participant’s home to perform the testing. In such cases, extra care was taken to ensure that the meeting was free from household distractions or interference from family members and pets.

At the beginning of each test session, participants were explained the entire test protocol and presented with the consent form (Appendix F). The researcher ensured that the consent form was fully understood and signed by each participant. They were then asked to complete a short demographic and health questionnaire, a brief mood assessment, and a series of cognitive tasks selected to target areas of cognition sensitive to changes in female estrogen levels. The cognitive tasks covered a comprehensive range of domains including verbal abilities, verbal, visual, working, and spatial memory, fine motor skills, perceptual speed, and spatial rotation. They were completed in the following order:

1. The Rey-Osterrith Complex Figure Test (RCF), Copy Trial
2. Controlled Oral Word Association Test (COWA)
3. RCF, Immediate Recall Trial
4. Logical Memory I (LM I)
5. Purdue Peg Board (PPB)
6. Mental Rotation Test (MRT), Parts I and II
7. RCF, Delayed Recall Trial
8. Logical Memory II (LM II)
9. Digit Symbol Subtest (DS)
10. Auditory Consonant Trigrams (ACT)
11. Object Location Memory (OLM)
12. Boston Naming Test (BNT)

Outcomes

The primary outcome measure in this study was performance on an immediate verbal memory task, as this task was likely to be affected by TAM based on previous research results. Performance scores obtained on the remaining cognitive tasks were designated as secondary outcome measures: delayed verbal memory, verbal fluency, verbal articulation, spatial memory, working memory, visual memory, fine motor skills, perceptual speed, and spatial rotation.

Assessment Measures

Demographic and Health Questionnaire

In order to ensure the equivalence of the two study groups in terms of demographic and health characteristics, a short multiple-choice questionnaire was developed specifically for this study (Appendix G). It was used to ask basic questions about each participant's demographic information and reproductive history. For example, participants were asked about their marital status, occupation, household income, and TAM use.
**Mood Assessment**

In order to ensure the equivalency of the two study groups in terms of their emotional state at the time of testing, the Profile of Mood States (POMS) (McNair, Lorr, & Droppelman, 1992) was used to measure each participant’s level of overall mood disturbance immediately prior to assessment. The POMS is frequently used to measure transient affective mood states in individual subjects (Spreen & Strauss, 1998). It contains 65 adjectives or short phrases such as miserable, tense, or sorry for things done. The participant is asked to rate all of these items based on how they have been feeling throughout the past week including the present day using a five-point Likert scale. Internal consistency of the six POMS factors are high, and range from 0.84 to 0.95. In addition, this questionnaire has been effectively used to measure psychological adjustment to breast cancer (Taylor, et al., 1985) and was therefore chosen to provide an accurate estimate of overall emotional state.

**Cognitive Assessment**

*Visual memory.* The Rey-Osterrith Complex Figure Test (RCF) (Meyers & Meyers, 1995) was used to assess immediate and delayed visual recall. In the task, the participant was first asked to copy a complex figure from a picture. After three and thirty minute delays, the participant was asked to draw the figure again from memory. The drawings produced are objectively scored based on the accuracy and placement of each individual component of the picture. Total scores were used for the copy, immediate, and delayed trials. The RCF is a commonly used measure with internal consistency ratings above $r = .60$ for the copy trial and above $r = .80$ for the recall trials (Spreen & Strauss,
In addition, performance has been previously shown to decrease with TAM use in breast cancer patients (Bender, et al., in press; Castellon, et al., 2004).

**Verbal fluency.** The written version of the Controlled Word Association Test (COWA, Spreen & Strauss, 1998) was used as a measure of verbal fluency. In the test, the participant was asked to write as many words as possible beginning with a certain letter of the alphabet in one minute. They were not allowed to write words that were also proper names or identical words with different endings (e.g., eat and eating). The test was scored according to the number of admissible words provided for each of three letters, including slang. For this study, a total score for all three letters was used to compare groups. The orally administered version of the COWA is a widely used measure of verbal fluency with high inter-rater reliability ($r = .70$) and moderate concurrent validity with other language tests ($r = .14 - .15$) (Spreen & Strauss, 1998). At least one study has reported that scores from the written version do not significantly differ from those of the oral one (Yeudall, Fromm, Reddon, & Stefanyk, 1986).

**Verbal memory.** The Logical Memory I (LMI) and Logical Memory II (LMII) subtests of the Wechsler Memory Scale, Third Edition (WMS-III, Wechsler, 1997a) were used to assess Immediate and Delayed verbal recall respectively. In LMI, the participant were read aloud two short paragraphs and asked to immediately recall all information that they could remember from the readings. In LMII, the participant was asked to recall the information after a 25-35 minute delay. A total score was obtained for each subtest. Both of these tests are primary scales of the WMS-III, and are accompanied by normative data from healthy individuals. The LMI and LMII have been shown to exhibit high internal consistency reliability in 45-54 year olds ($r = .89$ and $.82$ respectively) (Wechsler,
The LMI is also highly correlated with other tasks of verbal memory, including List 1-5 of the California Verbal Learning Test \((r = .66)\) (CVLT, Delis, et al., 1987), which indicates that it is a valid measure of verbal memory. In addition, it has been shown that women with breast cancer who were treated with adjuvant therapy scored lower on LMI than healthy controls (Jenkins, et al., 2004), making it an adequate measure for this population.

*Fine motor skills.* The Purdue Peg Board (PPB, Tiffin & Asher, 1948; Tiffin, 1968, Appendix H) was used to assess overall manual dexterity. Participants were asked to place as many narrow pegs down a row of small holes as they could with their right, left, and both hands in 30 seconds each. A total combined score was used to compare groups. The Purdue Peg Board Task has a moderate test-retest reliability within a single test session \((r = .60 - .76)\) (Tiffin, 1948), and has been shown to display sex differences in performance (Kimura, 1999; Spreen & Strauss, 1998). Furthermore, performance on the task has been shown to be sensitive to estrogen levels in both pre-menopausal women throughout the menstrual cycle, and post-menopausal women taking HRT (Kimura & Hampson, 1994). These findings suggest that it would also be an adequate measure for changes in dexterity as a result of TAM use.

*Spatial rotation.* The Mental Rotation Test (MRT, Vandenberg & Kuse, 1978, Appendix I) was used to assess the ability of participants to rotate a three dimensional object in mind. In the test, participants were asked to determine two correct depictions of a rotated target item. Two tests of ten items were completed in five minutes each, and then a total score was calculated. This task has been classically used to identify and measure sex differences in visuospatial abilities, and has been shown to have high
reliability in adults (Kuder-Richardson = .88) as well as moderate concurrent validity with other spatial tests (.32 - .68) (Vandenberg & Kuse, 1978; Kimura, 1999). In addition to the reliable male advantage observed on this task, researchers have also observed increased performance by females at low estrogen points in the menstrual cycle (Silverman & Phillips, 1993). Thus, MRT was also chosen as an adequate assessment of visuospatial abilities in TAM users compared to controls.

**Perceptual speed.** The Digit-Symbol (DS) subtest of the Wechsler Adult Intelligence Scale, Third Edition (WAIS-III, Wechsler, 1991) was used to as a measure of perceptual speed. In the task, participants were asked to match numbers with a set of symbols as quickly as possible within two minutes. Total scores were recorded. The DS was found to have high test re-test reliability in participants aged 45-54 years ($r = 0.91$) (Wechsler, 1997b). The DS was also found to be highly correlated to a processing speed factor ($r = 0.70$) (Wechsler, 1997b), which indicates that it is a valid measure for this type of cognitive ability. In addition, the DS was highly correlated (0.73) with other perceptual speed measures, such as the Symbol-Digit Modalities test. Performance on perceptual speed tasks including the DS also show sex differences and are sensitive to fluctuations in estrogen (Kimura, 1999).

**Working memory.** The Auditory Consonant Trigrams test (ACT) (Brown, 1958; Peterson & Peterson, 1959, Appendix J) was chosen as an increasingly difficult measure of working memory. The task required that participants recall three verbally presented letters while counting backwards from a number by threes for 0, 9, 18, or 36 seconds. A total score for all letters recalled correctly was obtained. There is some normative data available for adult performance on this task, and it seems to be relatively unaffected by
age and education level (Spreen & Strauss, 1998). To the knowledge of the author, however, there is no reliability or validity data available. Due to the evidence that increasingly difficulty working memory tasks may be facilitated by estrogen (Duff & Hampson, 2000; Keenan, et al., 2001), the ACT may be sensitive to TAM-related changes.

*Spatial memory.* The Object Location Memory (OLM, Eals & Silverman, 1994; Silverman & Eals, 1992, Appendix K) task was chosen as a measure of spatial memory. Participants were asked to examine an array of common objects for one minute, and then to determine which objects had changed places on a second array of the same objects. This measure has largely been used for research purposes and has not yet been validated or normed in healthy populations. Importantly, however, performance on this test has been shown to have a female advantage compared to males (Eals & Silverman, 1994; Silverman & Eals, 1992).

*Verbal articulation.* The Boston Naming Test (BNT, Kaplan, Goodglass, & Weintraub, 1983, Appendix L) was used to measure participants’ ability to articulate the names of objects. Participants were asked to name the objects as they decreased in familiarity (e.g., last item is ‘abacus’). A total score as well as the number of phonemic cues required were obtained for each participant. The BNT has been effectively used with normal adults, aging adults, adults with Alzheimer disease, and those with brain damage (Spreen & Strauss, 1998). The test has been shown to have high reliability ($r = .81$) when two equivalent forms were tested (Spreen & Strauss, 1998). It has also been moderately correlated with other verbal measures, such as the Verbal Comprehension Index of the WAIS-III ($r = .48$), and other memory measures, such as the Auditory Recognition
Delayed subtest of the WMS-III ($r = .39$) (Wechsler, 1997b). Although this particular test has not been used with cancer patients, there is some evidence to suggest that articulation scores may be lower in women using TAM (Eberling, et al., 2004).

**Determination of Required Sample Size**

The level of power for this study was set at 80% and the significance value at 0.05 (one-tailed due to the directional hypothesis) to test the main hypothesis regarding the effect of TAM use on immediate verbal recall. Previous research that looked at the effects of TAM use for cancer treatment on cognition (Jenkins, et al., 2004) found a mean raw score difference of 1.76 units between the adjuvant TAM group and the healthy control group on the primary outcome measure. In that study the SD was 3.97 for the patients and 4.59 for the controls. This resulted in an effect size between-group difference of approximately 0.40, a small to medium-sized effect. Using the same parameters, a total of 130 women were required for this study (65 for TAM and 65 for HC) to detect disparate performance scores between the TAM group and the HC group of $d = 0.40$ in immediate recall.

The recruitment of TAM users for this study was ultimately limited by the number of eligible participants that were residing locally at the time of the research. Therefore, our total sample was smaller in size than this ideal. Efforts were made to recruit equal numbers of age-matched HC participants and interim analyses were performed on the available data for this thesis. From this data, effect sizes were calculated to help determine if the expected differences are likely to be found, and to determine if a continuation with expanded recruitment is likely to be beneficial in terms of meeting statistical significance levels.
Statistical Methods

Where appropriate, two-tailed independent sample t-tests were used to compare demographic and health variables such as age, and number of months since cancer diagnosis. Other demographic variables were analyzed using chi-square analyses. A two tailed independent samples t-test was also used to test for equality between the groups on the mood assessment.

A one-tailed independent samples t-test was used to evaluate the effect of treatment (TAM use and HC) on test performance (immediate verbal recall scores). Similarly, a series of one-tailed independent sample t-tests were used to evaluate the effects of treatment on test performance for the remaining cognitive outcome measures individually. In order to assess the clinical relevance of any group differences, raw scores were converted to scaled or normative scores for all assessment measures in which normative data were available. Additional descriptive analyses were performed using these converted scores.

All statistical analyses were performed using the Statistical Package for the Social Sciences Version 14.0 (SPSS). The cut-off for statistical significance was designated at \( p = 0.05 \) for all statistical tests without correction for multiple comparisons; however, the exact significance values obtained will be reported for all analyses in order to appropriately evaluate their importance within the context of the other study results and previous research.
CHAPTER FOUR

Results

Demographics

The two groups were well matched on all of the demographic variables. Descriptive information regarding the distribution for each demographic variable for each group is shown in Table 1. There were no significant differences between the TAM group and the HC group in age ($p > 0.05$). There were also no significant differences observed between the groups in income, ethnicity, level of education, marital status, or employment status ($p > 0.05$).

Reproductive and Health Characteristics

There was no significant difference between the TAM ($M = 1.80, SD = 1.19$) and HC ($M = 1.40, SD = 1.01$) groups in the number of children they had given birth to, $t(38) = 1.15, p = .257$ (two-tailed), $d = .36$. Similarly, there was no difference between the TAM ($M = 248.90, SD = 331.07$) and HC ($M = 195.68, SD = 284.54$) groups in the length of time in months that they had used a hormonal birth control pill, $t(38) = .55, p = .59$ (two-tailed), $d = .17$.

Descriptive statistics for the health-related variables associated with breast cancer in the TAM group are shown in Table 2. Most women had received adjuvant therapy that included surgery, radiation, and TAM. All were diagnosed as having ER-positive cancer, and were taking 20mg/day of TAM at the time of the study.

Mood Assessment

For total mood disturbance on the POMS, there was no significant difference between the TAM group ($M = 12.65, SD = 21.37$) and the HC group ($M = 10.55, SD =$
21.37), \( t(38) = .33, p = .37 \) (one-tailed), \( d = .11 \). The scores for both groups fell within the normal range for this measure (McNair, et al. 1992).

**Neurocognitive Assessment**

Significantly lower scores were observed in the TAM group when compared to the HC group on three tasks: (a) verbal fluency, (b) perceptual speed, and (c) mental rotation. These results are presented in Table 3.

**Verbal fluency.** As hypothesized, when compared to the HC group \( (M = 39.65, SD = 10.67) \), the TAM group \( (M = 30.60, SD = 9.50) \) scored significantly lower on the verbal fluency task, \( t(38) = 2.83, p = 0.004 \) (one-tailed), \( d = 0.90 \). Specifically, the HC group was able to produce approximately nine (23%) more words in total than the TAM group. When compared with normative data corrected for age and education level of participants (Tombaugh, Kozak, & Rees, 1999), 55% \( (n = 11) \) of the participants in the TAM group scored below the 20th percentile on this task whereas only 25% \( (n = 5) \) of the HC group did.

**Perceptual speed.** On the DS, the TAM group scored significantly lower than the HC group as hypothesized (Table 3). In this timed task, the TAM group matched and copied approximately 10 (12%) fewer symbols than the HC group. When converted to scaled scores \( (M = 10, SD = 3) \) using the *Canadian Technical Manual for the WAIS-III* (Wechsler, 1997), the mean scaled score of the TAM group \( (M = 10.10, SD = 2.02) \) was significantly lower than that of the HC group \( (M = 11.95, SD = 2.56) \), \( t(38) = 2.53, p = 0.008 \) (one-tailed), \( d = 0.80 \). Although neither score falls outside of the Average ability range for the WAIS-III, there is a difference of approximately two scaled scores between the two groups.
Mental rotation. Contrary to what was hypothesized for this task, the TAM group $(M = 9.70, SD = 5.25)$ scored significantly lower than the HC group $(M = 13.70, SD = 7.56)$, $t(38) = 1.94, p = 0.01, d = 0.76$. The HC group answered an average of four (29%) more questions correctly than did the TAM group. Unfortunately, due to the empirical rather than clinical nature of this measure, to the knowledge of the researcher, there are no appropriate normative data available for comparison purposes.

The TAM group also had lower raw scores than HC group on 6 other tasks; however, these differences were not statistically significant ($p > .05$). Descriptive statistics, t-test results, and the effect sizes obtained for each of these measures are shown in Table 3. Although the results obtained for the remaining tasks were not statistically significant, small to moderate effect sizes were obtained for each measure (Table 3). Raw scores for each test were converted to normative scores for further comparison.

For the immediate and delayed visual recall tasks, standardized t-scores $(M = 50, SD = 10)$ were calculated using the normative data tables included in the *Rey Complex Figure Professional Manual* (Meyers & Meyers, 1995). The average scores for both groups fell within the normal range for both tests; however, the scores from 50% $(n = 10)$ of participants in the TAM group and 35% $(n = 7)$ of the HC group fell below the 25th percentile for immediate visual recall. Similarly, on the delayed visual recall task, 55% $(n = 11)$ of the TAM group and 45% $(n = 9)$ of the HC group scored below the 25th percentile.

Due to differences between the administration procedure used in this study and that contained in the WMS-III (Wechsler, 1997), standardized scaled scores could not be obtained for the immediate verbal task. However, the discrepancy in scores observed
between groups in this measure was equivalent to approximately 4 (15%) story units (e.g. Main character name, Characteristics of main character, story plot details, etc.). For each participant’s delayed verbal recall score, scaled scores ($M = 10, SD = 3$) were obtained from the *Wechsler Memory Scale-III Administration Manual* (Wechsler, 1997). The mean scaled scores for each group were within the Average ability range for the WMS-III, and the difference between groups was equivalent to approximately 1 scaled score.

Based on normative scores corrected for age and education (Tombaugh & Hubley, 1997), 47% ($n = 9$) of the TAM group and 21% ($n = 4$) of the HC group scored lower than the 25th percentile on the verbal articulation task. On average, the TAM group was able to correctly name 1-2 fewer objects than the HC group. The scores obtained on the fine motor skills task were not transformed due to a lack of published data for this purpose. Similarly, given the lack of performance disparity between groups on the working and spatial memory tasks, further analysis was not undertaken.
CHAPTER FIVE
Discussion

The object of the present study was to determine whether TAM had any influence on the cognitive abilities of pre-menopausal women who were using the drug for the adjuvant treatment of breast cancer. Based on reviews of the current literature, this is the first empirical study to investigate the effects of TAM in only pre-menopausal women, and exclusively from chemotherapy. When compared to age-matched healthy controls, TAM users exhibited significantly lower performance on tasks of verbal fluency, perceptual speed, and visuo-spatial ability. Although not statistically significant, group differences on tasks of immediate verbal memory and verbal articulation also provided support for the study hypotheses, in that moderate effect sizes were demonstrated in favour of healthy controls.

Interestingly, previous research has shown that lower levels of estrogen are associated with lowered performance on verbal fluency tasks (Hampson, 1990; Kimura, 1995), and that TAM may be associated with a similar lowered performance in women taking the drug in combination with chemotherapy compared to healthy controls (Castellon, et al., 2004). In combination with the present finding, these results suggest that the drug somehow interferes with estrogen-dependent processes normally required for some or all of these capabilities.

The women in the TAM group also performed significantly worse on the DS, a measure of perceptual speed. The lower scores observed in the TAM group, although still within the Average range for the task, suggests that the drug blocks the mediating effects of estrogen in the abilities required for optimal performance. Healthy, pre-menopausal
women score higher on tasks of perceptual speed than men do (Kimura, 1999), presumably due to the presence of estrogen. If this estrogen activity were blocked, such as it would be if TAM acts as an estrogen antagonist, then their task performance would be similarly impaired. This result has also been obtained in other studies. For example, Shilling, et al. (2003) observed significantly lower performance on a similar task of processing speed in post-menopausal women who were taking either TAM or Anastrozole (both of which interfere with normal estrogen activity) compared to healthy controls.

In contrast to hypotheses, women in the TAM group performed significantly worse than healthy controls on the MRT, a task of visuo-spatial rotation. It was expected that the lowered binding ability of estrogen in the women of the TAM group would positively influence scores obtained on the MRT, because the task is known to display a distinct male advantage as well as a reliance on presumably lower estrogen levels for ideal execution in healthy pre-menopausal women (Kimura, 1999). One possible reason for the discrepancy is that TAM reduced estrogen activity low enough that the TAM group exhibited scores similar to those observed when post-menopausal women complete the MRT (Kimura, 1995). The influence of TAM was much more substantial than observed differences that occur during the menstrual cycle. It is possible therefore, that the relationship between estrogen and visuo-spatial ability is U-shaped, with the lowest and highest levels being detrimental to task performance. Tamoxifen activity, subsequently, would cause such a detriment. No other studies, to the knowledge of the researcher, have utilized the MRT for TAM research. However, Castellon (2004) found that when compared to healthy controls, women who had taken TAM with chemotherapy
scored significantly lower on another test of visuo-spatial ability, the Block Design subtest of the WAIS-III, indicating that cognitive abilities in this domain may be affected by the drug. Additional research might include visuo-spatial tasks in order to further clarify the effects of TAM on these abilities.

It is also possible that the TAM users experienced significant declines on verbal fluency, perceptual speed, and visuo-spatial tasks because they were unable to focus their attention on the tasks, or to adequately self-monitor their progress throughout. In the MRT, for example, many women gave up soon after beginning the task and began to guess the answers. Similarly, others who gave a whole-hearted effort appeared to become frustrated with the task. During the COWA, some women appeared to the examiner as being surprised that they could not come up with any words. As a result, some women appeared to stop trying to generate them and waited for the time to run out. Although the same types of behaviours were occasionally observed in the HC group, they were not as common. This was ultimately reflected in the results for these tasks, suggesting an overall difficulty with its completion.

Although not statistically significant, moderate effects were also observed between groups on the immediate verbal memory ($d = 0.52$) and verbal articulation ($d = 0.49$) tasks. Although the testing of approximately 90 additional participants will be required in order to determine whether each of the effects actually exists, a discussion of their relative importance within the context of the present study is warranted here. The moderate effect observed in immediate verbal memory suggests that TAM may have also interfered with women’s ability to retain and recall verbally presented narrative information immediately after it is presented. Similar results have been obtained in
previous studies, where lowered estrogen was associated with decreased verbal memory ability in pre-menopausal (Phillips & Sherwin, 1992a; Sherwin & Tulandi, 1996), post-menopausal (Drake, et al., 2001), and women using TAM with chemotherapy (Castellon, et al., 2004). Shilling, et al. (2003) also found decreased immediate verbal memory performance associated with lowered estrogen in their study of post-menopausal women, but it is not clear whether these effects were due to TAM or Anastrozole.

Based on the preliminary results that have been obtained through the testing of a small portion of the originally calculated sample size required for small to moderate effects, it seems as though the anti-estrogen influence of TAM may have a negative effect on cognition such that there is a global decline in abilities. It is anticipated that once additional power is achieved, significant differences will be observed between pre-menopausal TAM users and healthy controls. It will be interesting to make this determination as such a result would provide the first convincing evidence in support of this hypothesis.

_TAM and Global Cognitive Decline_

The current findings, although preliminary, suggest that TAM has a widespread effect on the cognitive abilities of pre-menopausal women users that may be more pronounced than for post-menopausal women users. For example, Shilling, et al. (2003) found that TAM affected either perceptual speed or immediate verbal memory (cannot be specifically determined due to researchers being blind to treatment arms). Although these findings suggested that TAM has specific rather than global effects, it is more likely that the effects of TAM on certain cognitive domains are masked by the already existing lack of estrogen in menopausal women. Both the TAM users and healthy controls in the study

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1 Although lower performance was observed in this study, the results were not statistically significant.
would have already experienced and potentially adjusted to menopausal estrogen loss and would presumably be equivalent in any estrogen-related cognitive decline prior to the inception of TAM therapy. Overall effects of estrogen-loss would have already occurred, and would be near impossible to detect further differences. In contrast, the level of circulating endogenous estrogen in pre-menopausal women using TAM compared to pre-menopausal healthy controls is distinctly different.

In fact, using a cross-sectional design, Castellon, et al. (2004) found that women who used TAM scored significantly lower on tasks of verbal learning, visuo-spatial ability, and verbal fluency. When all test scores were combined for a global estimate, they found that TAM users were significantly lower than patients who had not received treatment. It must be noted that this study combined TAM with chemotherapy, and it was not explicitly stated whether the participants were pre- or post-menopausal (it likely that they were primarily pre-menopausal because they were aged 50 and younger). However, many of the tasks where differences were observed are similar to that of the present study, which did control for pre-menopausal status and cancer treatment. The fact that similar results as well as trends were observed between this and the present study provides additional support for the hypothesis that TAM affects cognition comprehensively in pre-menopausal women.

The contribution of estrogen to neurological processes is complex and therefore, it is difficult to completely explain the observed cognitive dysfunction. However, the potential mechanisms through which TAM, as an anti-estrogen, may have had a global effect on the cognitive abilities tested in the present study is through the regulation of neuronal structure and architecture. It has been determined that fluctuations in natural
estrogen levels modulate the connectivity of synapses throughout the brains of adult animals, with increases in estrogen resulting in increased numbers of synapses (Wooley & McEwen, 1992). Such modulation can have a large impact on cognitive abilities, as more synapses result in stronger, more efficient transmission of information from region to region. It is possible that TAM molecules act as antagonists to estrogen receptors (Birge, McEwen, & Wise, 2001), and in pre-menopausal women, this would make it impossible for naturally occurring estrogen molecules to bind. It seems likely that as a result, the estrogen-dependent synaptic density and associated signaling would decrease, and related cognitive abilities would decline.

Specifically, TAM could affect cognition through modulation of synapses in the basal forebrain, which projects its connections throughout the hippocampus and cortex (Sarter & Bruno, 1997). For example, estrogen plays a key role in the function of the cholingeric system, which is often associated with learning and memory. The ubiquitous neurotransmitter, acetylcholine, is required for signaling from the basal forebrain through to the cerebral cortex and hippocampus. Because estrogen mediates the amount of choline acetyl transferase, the enzyme required for the production of acetylcholine molecules available in the basal forebrain (McEwen & Alves, 1999), it is possible that TAM could inhibit this process. A substantial lack of acetylcholine in the brains of women taking TAM would therefore result in reduced signal transmission. Ultimately, this could manifest itself in decreased cognitive speed, accuracy, and fluency.

The widespread projections from the basal forebrain to other brain areas suggest that the cholinergeric system globally influences information processing. Previous research has found that when estrogen levels of pre-menopausal women were low, the strength
rather than the pattern of activation signals in the brain was significantly reduced
(Dietrich, et al., 2001). In addition, Eberling, et al. (2004) found decreased volume in the
hippocampus, as well as hypo-metabolism in the frontal lobes of TAM users. It could be
hypothesized, therefore, that a lack of endogenous estrogen would result in weakened
transmissions throughout the cortex, and ultimately the lowered cognitive performance of
women in the present study.

The results obtained in the present study also lend support to the hypothesis that
estrogen plays a crucial role in mediating activity in the pre-frontal cortex. Some studies
have shown that the use of lupron, an estrogen antagonist, results in wide-spread lack of
activity in this region (Berman, et al., 1997), and that this has an effect on tasks of
executive function (Grigorova, Sherwin, & Tulandi, in press). In the present study, the
significantly lower performance on the verbal fluency and perceptual speed tasks may
also indicate problems in executive functioning resulting from the pre-frontal cortex.
Verbal fluency tasks are dependent on this region (Weiss, et al., 2003), and are also
highly correlated with performance on the DS (Ruff, Light, Parker, & Levin, 1997),
suggesting that both of these tasks may be affected by reduced signal transmission in this
area. Therefore, the results of the present study suggest that the use of TAM, which
modulates the effects of estrogen receptors throughout the CNS, may subsequently result
in reduced signal strength throughout the pre-frontal cortex and ultimately a negative
effect on cognitive abilities related to executive function.

Alternately, it is possible that TAM had separate, yet wide-spread effects on
various brain regions, resulting in specific task decline. TAM will bind to either ER-α or
ER-β receptors throughout the brain, altering gene transcription differently in distant
anatomical areas or tissues. Such changes could have a variety of cellular effects, including changes in cell membrane structure or changes in cell function. If TAM acted through this mechanism, we would have expected to see single effects, measured by individual tasks that rely on specific anatomical regions of the brain. In addition, depending on the properties of the receptor that TAM bound to, we could have seen better or worse performance on the tasks. Although this explanation is possible, given the overall trend towards universal decline on the tasks tested, it seems unlikely. Much more research is required to investigate the role for estrogen and molecules like TAM in order to determine the exact processes associated with this mechanism. Additionally, testing more participants for the present study will help to identify whether specific domains are more susceptible than others, or whether the effects are actually comprehensive in nature.

Clinical Considerations

The clinical implications of the present study results are important for providing adequate information and care to pre-menopausal breast cancer patients and their families. In addition to being relevant to oncology practice, nursing care, and the provision of other health-related services, the considerations arising from the cognitive effects of TAM will be important for psychology professionals as well as employers. It is important to note that not all of the women in this study presented cognitive difficulties. However, the significantly lower group performance on the DS, MRT, and COWA tasks suggests that the effects of TAM are equivalent or worse than that of typical menopause. This will ultimately have an affect in the daily lives and activities of patients.

The lower verbal fluency scores of women using TAM in the present study are perhaps the most striking. Based on published norms (Tombaugh, Kozack, & Rees,
1999), more than half of the women \((n = 11)\) in the TAM group scored below the 20\(^{th}\) percentile for the COWA, which is equivalent to approximately 1 standard deviation below the mean and a low-average score classification (Spreen & Strauss, 1998). Only 25\% \((n = 5)\) of the HC group did fall within this range, indicating that a relatively large number of pre-menopausal women who are prescribed TAM experience difficulty in recalling specific words\(^2\). It is unlikely that this problem would be vocationally debilitating, but it could have a substantial impact on their typical functioning. In daily life, for example, women may not be able to readily access desired words. This could be even more apparent when the individual is required to think or respond quickly, or to recall specific information on command. For example, Paganini-Hill and Clark (2001) found that women who used TAM wrote significantly less verbally complex narratives than non-TAM users. This result, in combination with that of the present study seems to suggest that women using TAM are less able to articulate the desired words and as a result, may compensate through the composition of less complex speech and text.

In contrast to the HC group, who scored similarly to healthy college-aged females on the MRT (Vandenberg & Kuse, 1978), the TAM group answered 20\% (4) less questions correctly. This is the only known normative data published for the MRT, however, the decreased performance of TAM users in visuo-spatial abilities could also have real-world implications. The ability to effectively and efficiently rotate a three-dimensional object in mind has been associated with the ability to learn and navigate a map-based route (Kimura, 1999), suggesting that declines on this pencil-and-paper task might actually identify weaknesses in way finding, or perhaps even feelings of spatial

\(^2\) This should be interpreted with caution, as the published norms used were obtained using the oral version of the COWA.
disorientation that could result in falls or automobile accidents. An investigation of whether women feel as though they actually experience such changes was beyond the scope of the present study; however, the possibility remains open to future research. The possibility that women performed lower on this task due to executive function problems or attention difficulties could also have applications in daily life. Specifically, women may experience changes in their ability to multi-task, organize projects, or perform tasks that require a great deal of focus, detail, or micro-management.

From a clinical perspective, the lowered performance of the TAM group on the perceptual speed task was less pronounced. Importantly, although both groups scored within the Average classification range for the Wechsler tests, this does not suggest that women who begin using TAM would not experience some changes in their typical cognitive processing abilities. Given the demands of the task, it is likely that if women experienced changes in their cognition as a result of TAM, they would notice subtle inefficiencies in scanning text, noticing changes in visual stimuli, and learning and processing visually presented information. For example, it may be more difficult to notice errors in written work, or to remembering numbers or codes. Importantly, this would not necessarily represent a deficiency, but rather a subtle change in the capabilities that women were used to exhibiting.

It will be important for oncologists as well as other health care service providers to be aware of the potential cognitive effects and their manifestations in pre-menopausal women such that they can make appropriate hormonal treatment choices, as well as provide adequate information prior to taking the drug and acknowledgement of any effects after treatment begins. It may be especially important for this information to be
shared with women who may be susceptible to changes and/or would experience the greatest difficulty as a result of cognitive side effects.

On the one hand, it may be that women who lead cognitively stimulating lives may be at less of a risk for cognitive decline than those who do not. For example, Wilson, Barnes, and Bennet (2003) found that in an elderly population, those who reported more participation in activities with high cognitive demand throughout their lifetime (e.g. playing chess, reading, visiting a library, etc.) were less impaired on a comprehensive battery. This effect was more pronounced than it was for level of education, a lifestyle factor typically associated with cognitive abilities. On the other hand, it may be that these more active women do, in fact, experience cognitive problems when taking TAM but are less likely to report them. For example, women who hold highly demanding careers or report highly stressful lives may tend to under-attribute problems to TAM (Arnold, et al., 2001), and although they notice that they are impaired, do not think it is drug-related. Rather, these women tend to attribute the changes to their existing environment which is often hectic and stressful. This could cause additional problems for women, such as self-blame, frustration, and anxiety. Additional research might examine the relationships between pre-morbid lifestyle, intelligence, and TAM-related cognitive difficulty.

It is also possible that knowledge of, access to, and use of cognitive strategies could be useful in alleviating the changes associated with TAM. Such strategies might be helpful in providing support for users. For example, Gunther, Schafer, Holzner, and Kemmler (2003) found that computer training programs were highly effective in increasing the cognitive test scores of elderly long-term care patients. Using practice tasks like creating words from anagrams, answering questions following reading a
paragraph or story, splitting lines into two equal parts, and perceptual speed tasks significantly increased the test scores of participants in verbal memory, visual memory, processing speed, and learning. Similar practice might help to alleviate TAM-related difficulty.

The clinical manifestations of TAM use described here are certainly not meant to be exhaustive; the cognitive effects of TAM, especially if they do prove to be global, would be widespread and have a number of real-life applications. Such effects will undoubtedly be different, as there was considerable variability in the scores achieved by participants in the TAM group of the present study; however, there is a large potential for any cognitive changes to become problematic depending on the patient’s past experiences, their current livelihood and lifestyle, and their knowledge and use of alternate strategies and coping mechanisms.

Limitations of the Present Study

Despite the care taken to control for between group differences, the interpretation of the present study results are limited by the lack of a breast cancer control group that had not received hormonal treatment, the possible cognitive effects of radiation or surgery, the cross-sectional design, the lack of a pre-test measurement of overall IQ, and the lack of an adequate sample size for the detection of additional effects.

First, it is impossible to determine whether outside of any treatment, having breast cancer itself alters cognition compared to individuals who have not had breast cancer. Attempts were made in the present study to control for the possible influence of mood and fatigue on cognitive abilities, as women with breast cancer have been shown to exhibit increased mood symptoms after diagnosis (Epping-Jordan, et al., 1999; Turner, et
al., 2005). There were no differences observed between the two groups of the present study on this construct, but it is possible that additional effects of cancer influenced the cognitive abilities of the women in the TAM group. It could also be the case that the physiological effects of the cancer process itself may influence cognition, but no research is available on this topic. The addition of a control group comprised of women who had received surgery for breast cancer but not taken TAM would help to elucidate any of these issues.

In addition, despite the exclusion of chemotherapy treatment in order to control for its potential cognitive effects, it is also difficult to determine whether the patients in this study exhibited deficits as a result of their radiation therapy or surgery. Cognitive effects as a result of treatment are of growing concern (Wefel, Kayl, & Meyers, 2004), and although it seems unlikely that the local radiation therapy or anesthesia received by the women in the present study would have long-lasting effects on their cognitive abilities, it cannot be conclusively refuted in the present study.

The cross-sectional design that was utilized in this study also limits the conclusions that can be drawn. Although the two study groups were well matched in terms of their mood, age, and demographic information, it is impossible to conclude with certainty that the differences in their cognitive abilities were due to TAM. For example, it is possible that the women in the HC group exhibited a higher level of intellect, or some other inherent personality trait rendering them better apt to complete cognitive tests. More accurate information would be obtained through a longitudinal design in which women were tested prior to their surgery, radiation, and hormonal treatment, a few
months after their treatment began and finally some time after this. This would provide a tightly controlled analysis of the individual effects of TAM.

It is also important to acknowledge that there was no pre-assessment of intellect to ensure that the two study groups were matched in their overall IQ. Thus, it is possible that the differences obtained between the groups on the cognitive measures were not a result of the TAM, but the result of different pre-morbid intellectual capabilities that would over-arch the specific domains tested. Although the relative equality between the study groups was achieved in terms of age, education, and socio-economic status, inherent differences between the two groups in terms of intelligence cannot be dismissed. A future study would be wise to incorporate a quick measure to control for such confounds. For example, the Wechsler Abbreviated Scale of Intelligence (WASI, Wechsler, 1999), a condensed version of the WAIS, provides a short, reliable measure of overall intelligence.

It is unfortunate that the required number of participants could not be accessed and that as a result, the small-moderate effect sizes obtained in many of the study tasks did not reach statistical significance. Due to the importance of excluding participants who had received chemotherapy treatment, the potential recruitment pool was limited. Although this limitation was beyond the control of the researcher, efforts are currently being made to expand recruitment to another urban centre where it is expected that a similar number of participants will be eligible. It is expected that testing these individuals will provide the additional evidence required to determine whether TAM has a global effect on the cognitive abilities of pre-menopausal patients. In addition, due to the low power associated with our small sample size, no corrections were made for the multiple t-
tests performed. The estimated overall probability of making at least one Type I error in this study was 0.40 (Stevens, 2002); however, this risk was assumed in order to avoid the even greater risk of making a Type II error.

Future Directions for Research

It will be imperative for future research to confirm the hypothesis that TAM has global cognitive effects. Such studies should work to incorporate the strengths of previous ones. For example, longitudinal designs that control for menopausal status, the effects of chemotherapy, the effects of oral contraceptive medication, and pre-test IQ would be ideal.

Another consideration for future research would be to include some specific measures of executive function and attention. It is possible that the seemingly global decline in cognitive abilities could have been due to executive function, which is involved in the verbal fluency, perceptual speed, and visuo-spatial rotation tasks used in the present study. The same is true of the ability to focus attention. Future studies that include measures to assess these two cognitive processes would help to identify whether any global dysfunction associated with TAM was due to either of them having an overall effect, or was actually due to specific difficulties.

Prolonged TAM use should also be studied in terms of increased susceptibility of patients to Alzheimer disease (AD) and dementia. It is known that AD occurs more frequently in women due to the lack of estrogen associated with menopause (Birge, et al., 2001). Although a recent study of over 2800 post-menopausal women has revealed that there may be an overall adverse effect of HRT on global cognitive function (Espeland, et al., 2006), other studies have shown that when women take HRT early on in menopause,
while estrogen receptors are still intact, the risk of AD is reduced (see Brinton, 2004). It is possible, therefore, that pre-menopausal women, who begin reducing the estrogen activity in the brain prior to natural menopause, would be at an increased risk for such diseases. Epidemiological studies such as this one would not be difficult, seeing as a large number of women have finished the five year duration of TAM treatment at this time.

Summary & Conclusion

In sum, the results of the present study suggest widespread cognitive decline associated with TAM use for the hormonal treatment of breast cancer in pre-menopausal women. Due to the presence of natural estrogen in the bodies of these women, it is proposed that the blockage of estrogen receptors in their brains is more prominent than it would be in post-menopausal women. Deficits may have a moderate impact on the daily functioning of women users; specifically in areas that require the generation and articulation of words, the perception and learning of visual information, and the manipulation of visuo-spatial stimuli. Such deficits should be considered important for the determination of appropriate treatments for patients with breast cancer, the provision of adequate information regarding side-effects, and when acknowledging reports of cognitive difficulties.
Table 1

*Group Descriptive Statistics for Demographic Variables*

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Group</th>
<th></th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TAM</td>
<td>(n = 20)</td>
<td></td>
<td>HC</td>
<td>(n = 20)</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td>M</td>
<td>SD</td>
<td></td>
</tr>
<tr>
<td>Age (Years)</td>
<td>45.91</td>
<td>2.88</td>
<td>45.05</td>
<td>2.74</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Yearly Household Income</th>
<th>n</th>
<th>%</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;$60,000</td>
<td>10</td>
<td>50</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>$60,000 – 74,999</td>
<td>1</td>
<td>5</td>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>$75,000 – 99,999</td>
<td>2</td>
<td>10</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>&gt; $100,000</td>
<td>7</td>
<td>35</td>
<td>10</td>
<td>50</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th></th>
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<tbody>
<tr>
<td>Caucasian</td>
<td>17</td>
<td>85</td>
<td>19</td>
<td>95</td>
</tr>
<tr>
<td>Asian (or Pacific Islander)</td>
<td>2</td>
<td>10</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Latina</td>
<td>1</td>
<td>5</td>
<td>0</td>
<td>0</td>
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Table 1 (cont.)

<table>
<thead>
<tr>
<th>Education (Highest Level)</th>
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<tbody>
<tr>
<td>Grade 7-12</td>
<td>1</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>High School</td>
<td>2</td>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vocational Training</td>
<td>2</td>
<td>10</td>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>Some college/university</td>
<td>4</td>
<td>20</td>
<td>5</td>
<td>25</td>
</tr>
<tr>
<td>College/university graduate</td>
<td>5</td>
<td>25</td>
<td>7</td>
<td>35</td>
</tr>
<tr>
<td>Masters degree</td>
<td>4</td>
<td>20</td>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>Doctorate degree</td>
<td>2</td>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Marital Status</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Married or living together</td>
<td>14</td>
<td>70</td>
<td>15</td>
<td>75</td>
</tr>
<tr>
<td>Never Married</td>
<td>1</td>
<td>5</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Separated</td>
<td>1</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Divorced</td>
<td>3</td>
<td>15</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Widowed</td>
<td>1</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Unmarried, have lived together</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>5</td>
</tr>
</tbody>
</table>
Table 1 (cont.)

<table>
<thead>
<tr>
<th>Employment Status</th>
<th>13</th>
<th>65</th>
<th>10</th>
<th>50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Working full-time</td>
<td>13</td>
<td>65</td>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>Working part-time</td>
<td>4</td>
<td>20</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Unemployed</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Homemaker</td>
<td>1</td>
<td>5</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Other (self-employed, student)</td>
<td>2</td>
<td>10</td>
<td>4</td>
<td>20</td>
</tr>
</tbody>
</table>
Table 2

*Descriptive Statistics for Health Characteristics in the TAM Group*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TAM Group (n = 20)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>Cancer Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>17</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>3</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Type of Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery + TAM</td>
<td>7</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>Radiation + TAM</td>
<td>1</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Surgery &amp; Radiation + TAM</td>
<td>12</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Length of Time Since Diagnosis (Years)</td>
<td>3.17</td>
<td>1.47</td>
<td></td>
</tr>
<tr>
<td>Length of TAM Use (Years)</td>
<td>2.44</td>
<td>0.96</td>
<td></td>
</tr>
</tbody>
</table>
Table 3

*Descriptive Statistics and Effect Sizes for Neurocognitive Assessment Task Raw Scores Obtained in the TAM and HC Groups*

<table>
<thead>
<tr>
<th>Task</th>
<th>Group</th>
<th>Statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TAM (n = 20)</td>
<td>HC (n = 20)</td>
</tr>
<tr>
<td>Verbal Fluency (COWA)</td>
<td>30.60 (9.50)</td>
<td>39.65 (10.67)</td>
</tr>
<tr>
<td>Perceptual Speed (DS)</td>
<td>72.25 (12.91)</td>
<td>82.15 (13.93)</td>
</tr>
<tr>
<td>Mental Rotation (MRT)</td>
<td>9.70 (5.25)</td>
<td>13.70 (7.56)</td>
</tr>
<tr>
<td>Immediate Visual Memory (RCF)</td>
<td>17.60 (5.85)</td>
<td>19.53 (5.22)</td>
</tr>
<tr>
<td>Variable</td>
<td>Mean 1</td>
<td>Mean 2</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td>Delayed Visual Memory (RCF)</td>
<td>17.03</td>
<td>19.03</td>
</tr>
<tr>
<td>Immediate Verbal Recall (LMI)</td>
<td>23.85</td>
<td>27.40</td>
</tr>
<tr>
<td>Delayed Verbal Recall (LMII)</td>
<td>21.55</td>
<td>24.00</td>
</tr>
<tr>
<td>Fine Motor Skills (PPD)</td>
<td>40.70</td>
<td>42.10</td>
</tr>
<tr>
<td>Verbal Articulation (BNT)</td>
<td>55.42</td>
<td>56.95</td>
</tr>
<tr>
<td>Working Memory (ACT)</td>
<td>46.10</td>
<td>46.50</td>
</tr>
</tbody>
</table>
Table 3 (cont.)

<table>
<thead>
<tr>
<th>Spatial Memory (OLM)</th>
<th>21.00</th>
<th>20.66</th>
<th>34</th>
<th>0.34</th>
<th>0.37</th>
<th>0.16</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(3.00)</td>
<td>(3.09)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*One person in each group did not complete the BNT, thus the total sample size for each group is 19.

*Due to unequal variance between groups, a corrected degrees of freedom were used.

*Four HC participants did not complete this task, thus the total sample size for this group is 16.

*p<0.05, one-tailed. **p<0.01, one-tailed.
REFERENCES


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Cognitive Effects of Tamoxifen


Osterlund, M. K., Gustafsson, J., Keller, E., & Hurd, Y. L. (2000). Estrogen receptor β (ERβ) messenger ribonucleic acid (mRNA) expression within the human
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van Dam, F. S. A. M., Schagen, S. B., Muller, M. J., Boogerd, W., van der Wall, E.,
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Psychological Corporation.

Psychological Corporation.

Psychological Corporation.

Toronto, ON: The Psychological Corporation.


APPENDIX A: ETHICS APPROVAL

2005-11-30

Dr. L.E. Carlson
Department of Oncology
Tom Baker Cancer Centre
Calgary, Alberta

Dear Dr. Carlson:

Re: Cognitive Effects of Tamoxifen in Premenopausal Women with Breast Cancer Compared to Healthy Controls.

Grant ID: 18877

MSc Student: Palmer, Jaime

The above-noted proposal, including the Research Proposal, the Telephone Pre-Screening Protocol, the Demographics and Reproductive History Questionnaire, the Recruitment Ad, the Online Poster (Version dated November 29, 2005), and the Participant Consent Form (Version 1, dated November 15, 2005) has been submitted for Committee review and found to be ethically acceptable.

Please note that this approval is subject to the following conditions:
(1) appropriate procedures for consent for access to identified health information has been approved;
(2) a copy of the informed consent form must have been given to each research subject, if required for this study;
(3) a Progress Report must be submitted by 2006-11-30, containing the following information:
   i)  the number of subjects recruited;
   ii) a description of any protocol modification;
   iii) any unusual and/or severe complications, adverse events or unanticipated problems involving risks to subjects or others, withdrawal of subjects from the research, or complaints about the research;
   iv) a summary of any recent literature, finding, or other relevant information, especially information about risks associated with the research;
   v) a copy of the current informed consent form;
   vi) the expected date of termination of this project.
(4) a Final Report must be submitted at the termination of the project.

Please note that you have been named as a principal collaborator on this study because students are not permitted to serve as principal investigators. Please accept the Board's best wishes for success in your research.

Yours sincerely,

Glenys Godlovič, PhD

Associate Chair, Conjoint Health Research Ethics Board

OFFICE OF MEDICAL BIOETHICS
Room 93, Heritage Medical Research Bldg
3330 Hospital Drive NW
Calgary, AB, Canada T2N 4N1
Telephone: (403) 220-7990
Fax: (403) 283-8524
Email: omb@ucalgary.ca

Dr. G. Browman (information)
Office of Information & Privacy Commissioner
Ms. M. Payne (Centre for Advancement of Health)

Research Services
Ms. J. Palmer (MSc Student)

Ms. Gail Corbett (Communications & Fund Development)
Female Participants Wanted!!

U of C Masters student is doing a study on MEMORY and related abilities. Looking for women who are:

- Pre-menopausal
- Aged 30-50
- Not taking birth control pills or other hormones

Total time commitment is ONLY 1-1.5 hours and testing times are flexible.

Memory Study
Jaime @ 836-6476
jpalme@ucalgary.ca
**APPENDIX C: ONLINE RECRUITMENT ADVERTISEMENT**

<table>
<thead>
<tr>
<th>* Surname of Principal Investigator: Carlson</th>
</tr>
</thead>
<tbody>
<tr>
<td>* Study Title: Cognitive Effects of Tamoxifen in Premenopausal Women with Breast Cancer Compared to Healthy Controls</td>
</tr>
<tr>
<td>* GRANT-ID: 18877</td>
</tr>
</tbody>
</table>

**Study Description:** We are conducting a research study of the effects of the anti-estrogen drug, Tamoxifen, on the cognitive abilities of women with early breast cancer. We are looking for **healthy premenopausal women** to participate in the study as part of a comparison group. If you choose to participate, you will be asked to come to the Tom Baker Cancer Centre **once** for about 1-1.5 hours to participate in a brief individual interview, and to complete a selection of psychological tests.

**Inclusion Criteria #1:** Premenopausal Status

Inclusion Criteria #2:

Inclusion Criteria #3:

Inclusion Criteria #4:

Inclusion Criteria #5:

**Exclusion Criteria #1:** Use of any hormonal drugs such as birth control

Exclusion Criteria #2: Current or history of breast cancer

Exclusion Criteria #3:

Exclusion Criteria #4:

Exclusion Criteria #5:

* **Keyword #1:** breast cancer  
  **Keyword #2:** tamoxifen  
  **Keyword #3:** memory  
  **Keyword #4:** cognition  
  **Keyword #5:** estrogen  
  **Keyword #6:**

* **Contact Information:** Jaime Palmer @ 355-3213 OR jpalme@ucalgary.ca
APPENDIX D: MAGAZINE RECRUITMENT ADVERTISEMENT

Research Volunteers Needed!

We are looking for women aged 30-50, who do not have cancer, and are not taking hormonal birth control to help in our study of the effects of cancer treatment on memory, fine motor skills, spatial ability, and verbal ability. These women will help us to compare with a group of cancer survivors.

For more information call 355-3214 or email jpalme@ucalgary.ca
APPENDIX E: PRE-SCREENING PROTOCOL

Tamoxifen and Cognition Research Study
Telephone Pre-screening Protocol

<table>
<thead>
<tr>
<th>Today's Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name</td>
</tr>
<tr>
<td>Date of Birth</td>
</tr>
<tr>
<td>ACB Number</td>
</tr>
<tr>
<td>Type of Primary Cancer Diagnosis</td>
</tr>
<tr>
<td>Estrogen receptor type (i.e. positive or negative – if known)</td>
</tr>
<tr>
<td>Stage of Cancer (i.e. I, II, III, IV – if known)</td>
</tr>
<tr>
<td>Date of Most Recent Cancer Diagnosis</td>
</tr>
<tr>
<td>Are you currently taking Tamoxifen?</td>
</tr>
<tr>
<td>Approximate duration of Tamoxifen use (in months)?</td>
</tr>
<tr>
<td>Type of Cancer Treatment(s) (i.e. surgery, radiation, chemotherapy, etc)</td>
</tr>
<tr>
<td>Treatment Start Date(s) (Please specify for each treatment)</td>
</tr>
<tr>
<td>Treatment End Date(s) (Please specify for each treatment)</td>
</tr>
<tr>
<td>Question</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>What medications are you currently taking? (please list name of medication and dosage, if known)</td>
</tr>
<tr>
<td>Have you ever been diagnosed with, or received treatment for, emotional or psychiatric problems?</td>
</tr>
<tr>
<td>(IF YES:) Please describe the nature of the problem(s) and time frame:</td>
</tr>
<tr>
<td>Are you currently using birth control or any other hormonal manipulations drugs?</td>
</tr>
<tr>
<td>Approximate number of months since last time you used birth control?</td>
</tr>
<tr>
<td>Approximate Date of your last menstrual period?</td>
</tr>
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APPENDIX F: CONSENT FORM

TOM BAKER CANCER CENTRE

DEPARTMENT OF PSYCHOSOCIAL RESOURCES
1331 - 29 Street N.W., Calgary, AB T2N 4N2
Phone: (403) 944-1767 Fax: (403) 283-6032

Cognitive Effects of Tamoxifen in Premenopausal Women with
Breast Cancer Compared to Healthy Controls

Principal Investigator: Dr. Linda Carlson
Co-Investigators: Jaime Palmer, Masters Student, Dr. Tara Power,
And Dr. Theresa Trotter

Consent Form

This consent form, a copy of which has been given to you, is only part of the process of
informed consent. It should give you the basic idea of what the research project is about
and what your participation will involve. If you would like more details about something
mentioned here, or information not included here, you should feel free to ask. Please
take the time to read this carefully and to understand any accompanying information.

Purpose:

The purpose of this study is to investigate the cognitive effects that may be associated
with the use of the drug, Tamoxifen, commonly used to treat and prevent breast cancer.
We are interested in obtaining information about memory, motor skills, spatial skills, and
verbal abilities.

The information that we hope to gain as a result of this study will be important in
increasing our knowledge of symptoms associated with hormone therapy in cancer. This
study will also help to advance our knowledge of the connections between the body and
the mind.

You will be asked to participate in one of two groups, depending on your current
Tamoxifen use: 1) Tamoxifen for adjuvant breast cancer therapy; 2) No Tamoxifen use.
All participants will be asked to complete the same tasks in this study. The only difference between the three groups is the level of Tamoxifen currently used.

**Procedures:**

Participation in this study involves one session which will last approximately 1 - 1.5 hours.

All participants from each of the two study groups will be asked to meet individually for an interview and testing. You will be asked to make one, 1 – 1.5 hour visit to the Tom Baker Cancer Centre. During this meeting, you will be asked to participate in the following:

1) The completion of short questionnaire in which you will be asked about your personal and reproductive history. This will take about 10 minutes.

2) The completion of a short mood assessment questionnaire. This will take 5-10 minutes.

3) The completion of ten psychological tasks that vary in the amount of time they require. No individual task will take longer than 30 minutes to complete, and breaks will be provided as needed. These are not like tests in school where there are clear right and wrong answers – we just want to see how you are typically doing on these tasks that are similar to things that you have to do everyday. The psychological tasks will include:
   a) Verbal tasks that examine things like speaking out loud and naming objects
   b) Memory tasks that examine your ability to remember things such as objects and words
   c) Perceptual tasks such as matching symbols with numbers
   d) A task that examines your manual dexterity. This will involve moving and placing small objects with your hands.

No adverse effects to you as a result of this study are expected to occur. The tasks have been designed to replicate natural abilities and skills, and therefore are unlikely to cause discomfort greater than daily stress experienced in your normal life. The medical care that you receive will not in any way be affected by whether you choose to participate in this study or not. Your participation is entirely voluntary and you may choose to stop participating at any time.

To check the personal and medical information you give us, we will be accessing your patient information (i.e., health records) if you are in the breast cancer patient group. **By signing this form, you will be allowing access to your existing patient information, for this study.** The only people who will have access to your patient information will be the Principle and Co-investigators. No identifying information will be released to anyone other than the project investigators listed above.
Compensation:

The study is estimated to be complete by April, 2006. After completion of the study, we will mail you an information brochure presenting our main findings.

In the event that you suffer injury as a result of participating in this research, no compensation will be provided for you by the Canadian Institutes of Health Research, the University of Calgary, the Calgary Health Region, the Alberta Cancer Board or the Researchers of this study. You still have all your legal rights. Nothing said here about treatment or compensation in any way alters your right to recover damages.

Confidentiality:

If you participate, your reports may be made available in academic and professional venues (e.g., conference presentations and journal articles) and to the Tom Baker Cancer Centre, the sponsors of this study. However, you will not be identified as an individual in any report coming from this study. This means that no record bearing your name will be provided to anyone else except the investigators involved in this study.

All material and data obtained from this study will be stored and may be used for future analysis without obtaining further consent from you. However, each study arising as a result of information obtained through this research will be submitted for ethical approval.
Your signature on this form indicates that you have understood to your satisfaction the information regarding your participation in the research project and agree to participate as a subject. In no way does this waive your legal rights nor release the investigators, sponsors, or involved institutions from their legal and professional responsibilities. You are free to withdraw from this study at any time without jeopardizing your health care. Your continued participation should be as informed as your initial consent, so you should feel free to ask for clarification or new information throughout your participation. If you have further questions concerning matters related to this research, please contact Dr. Linda Carlson at 944-1712.

If you have any questions concerning your rights as a possible participant in this research, please contact Pat Evans, Associate Director, Internal Awards, Research Services, University of Calgary, at 220-3782.

Name of Participant

Signature of Participant ___________________________ Date __________

Name of Witness

Signature of Witness ___________________________ Date __________

Name of Principal Investigator

Signature of Principal Investigator ___________________________ Date __________

A copy of this consent form will be given to you. Please keep it for your records and future reference.
APPENDIX G: DEMOGRAPHIC AND HEALTH QUESTIONNAIRE

Tamoxifen and Cognition Research Study
Investigators:
Dr. Linda Carlson, Jaime Palmer (M.Sc. Student), and Dr. Tara Power

Patient Questionnaire

Thank you for participating in this pre-screening. Your assistance will help us learn more about how people like yourself perform on tasks of memory, motor function, and verbal abilities.

All of the information you provide will be kept strictly confidential.

Your answers are very important to us. Please answer all questions as honestly as you can.

Thank you for your time and cooperation.
DEMOGRAPHICS

1. **Your date of birth:** ______________________
   
   *Month / Day / Year*

2. **How would you describe your primary racial or ethnic group?**
   - White, Caucasian
   - Black, African American
   - Native American, Eskimo, Aleut
   - Asian or Pacific Islander
   - Hispanic, Latino
   - Other → Specify ______________________

3. **What is the highest grade or year of school you have completed?**
   - No formal education
   - Grade 1
   - Grade 2
   - Grade 3
   - Grade 4
   - Grade 5
   - Grade 6
   - Grade 7
   - Grade 8
   - Grade 9
   - Grade 10
   - Grade 11
   - Grade 12 / High school diploma / GED (General Education Diploma)
   - Vocational training after high school
   - Some college / associate degree
   - College graduate (4 or 5 year program)
   - Master's degree (or other post-graduate training)
   - Doctoral degree (PhD, MD, EdD, DVM, DDS, JD, etc.)
4. *Which of the following best describes your marital status?*

- O currently married and living together, or living with someone in a marriage-like relationship
- O never married
  
  - O place an "X" over this circle if you have ever lived with someone in a marriage-like relationship
- O separated
- O divorced
- O widowed

**EMPLOYMENT**

5. *What is your current employment status? Check ALL that apply.*

- O Working full time for pay ➔ number of hours per week ______
- O Working part time for pay ➔ number of hours per week ______
- O Not currently employed, looking for work
- O Retired
- O Homemaker
- O Disabled (Not working because of a permanent or temporary disability)
- O Other (please, specify): ________________________________

6. *Please describe your occupation(s) throughout the past five years (i.e. teacher, customer service, etc.):*

_________________________________________________________________________
_________________________________________________________________________
_________________________________________________________________________
7. **Which category best describes your yearly household income before taxes?**

Do not give the dollar amount, just give the category. Include all income received from employment, social security, support from children or other family, welfare, Aid to Families with Dependent Children (AFDC), bank interest, retirement accounts, rental property, investments, etc.

<table>
<thead>
<tr>
<th>Income Range</th>
<th>Selection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than $5,000</td>
<td>O</td>
</tr>
<tr>
<td>$5,000-$9,999</td>
<td>O</td>
</tr>
<tr>
<td>$10,000-$14,999</td>
<td>O</td>
</tr>
<tr>
<td>$15,000-$19,999</td>
<td>O</td>
</tr>
<tr>
<td>$20,000-$29,999</td>
<td>O</td>
</tr>
<tr>
<td>$30,000-$39,999</td>
<td>O</td>
</tr>
<tr>
<td>$40,000-$49,999</td>
<td>O</td>
</tr>
<tr>
<td>$50,000-$59,999</td>
<td>O</td>
</tr>
<tr>
<td>$60,000-$74,999</td>
<td>O</td>
</tr>
<tr>
<td>$75,000-$99,999</td>
<td>O</td>
</tr>
<tr>
<td>$100,000-$124,000</td>
<td>O</td>
</tr>
<tr>
<td>$125,000-$149,000</td>
<td>O</td>
</tr>
<tr>
<td>$150,000 or more</td>
<td>O</td>
</tr>
</tbody>
</table>

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**REPRODUCTIVE HISTORY**

8. **How many children have you given birth to?**

- O 0
- O 1
- O 2
- O 3
- O 4
- O 5
- O 6
- O 7
- O More than 7
9. Have you ever taken birth control pills?

O Yes
O No

If Yes, for how long?

TAMOXIFEN USE (IF APPLICABLE)

10. Are you currently taking Tamoxifen?

O Yes
O No

11. If you answered yes to Question # 10, have you noticed any changes in your mood?

O Yes
O No

Please Describe:

12. If you answered yes to Question # 10, have you noticed any changes in your behaviour (i.e. memory, concentration, etc.)?

O Yes
O No

Please Describe:
APPENDIX H: PURDUE PEG BOARD

Purdue Peg Board Test

ID: ____________

Preferred Hand: R L

Time Given: 1 Minute

Total Number of Pins Inserted with Preferred Hand: ____________

Total Number of Pins Inserted with Non-Preferred Hand: ____________

Total Pairs of Pins Inserted with Both Hands: ____________
APPENDIX I: MENTAL ROTATION TEST

Name ____________________________
M.R.T. Test
Date ____________________________

This is a test of your ability to look at a drawing of a given object and find the same object within a set of dissimilar objects. The only difference between the original object and the chosen object will be that they are presented at different angles. An illustration of this principle is given below, where the same single object is given in five different positions. Look at each of them to satisfy yourself that they are only presented at different angles from one another.

![Illustration]

Below are two drawings of new objects. They cannot be made to match the above five drawings. Please note that you may not turn over the objects. Satisfy yourself that they are different from the above.

![New objects]

Now let's do some sample problems. For each problem there is a primary object on the far left. You are to determine which two of four objects to the right are the same object given on the far left. In each problem always two of the four drawings are the same object as the one on the left. You are to put Xs in the boxes below the correct ones, and leave the incorrect ones blank. The first sample problem is done for you.

![Sample problems]

Go to the next page

Adapted by S. G. Vandenberg, University of Colorado, July 15, 1971
Revised instructions by H. Crawford, U. of Wyoming, September, 1979
Images digitized and reprinted by Susanna Douglas, University of Texas, March, 1996

*This is a public domain document and does not require copyright permission.*
Do the rest of the sample problems yourself. Which two drawings of the four on the right show the same object as the one on the left? There are always two and only two correct answers for each problem. Put an X under the two correct drawings.

1. [Drawings]
   - [ ]
   - [ ]
   - [ ]
   - [ ]

2. [Drawings]
   - [ ]
   - [ ]
   - [ ]
   - [ ]

3. [Drawings]
   - [ ]
   - [ ]
   - [ ]
   - [ ]

Answers: 1. first and second drawings are correct
         2. first and third drawings are correct
         3. second and third drawings are correct

This test has two parts. You will have 3 minutes for each of the two parts. Each part has two pages. When you have finished Part I, STOP. Please do not go on to Part 2 until you are asked to do so. Remember: There are always two and only two correct answers for each item.

Work as quickly as you can without sacrificing accuracy. Your score on this test will reflect both the correct and incorrect responses. Therefore, it will not be to your advantage to guess unless you have some idea which choice is correct.

DO NOT TURN THIS PAGE UNTIL ASKED TO DO SO.
APPENDIX J: AUDITORY CONSONANT TRIGRAMS

Auditory Consonant Trigrams – Score Sheet

Instructions (Read aloud to participant)

I am going to say three letters of the alphabet, and I would like you to remember them. When I signal you like this (knock on table), I would like you to tell me what the letters were. Sometimes, after I say the letters, I would like you to begin counting backwards from a number by threes, like this 100, 97, 94, etc. I will tell you which number I would like you to start from, and I would like you to continue counting until I signal you to tell me the letters. When you hear the knock, please say the three letters.

Let's try one as a practice: "F... D... B... 98... 95... 93..."

Yes, that is right. Count backwards with me until I knock. Then tell me the letters. Are you ready? Ok, let's begin.

<table>
<thead>
<tr>
<th>Consonant</th>
<th>1st Number</th>
<th>Delay (sec)</th>
<th>Response</th>
<th># Correct</th>
</tr>
</thead>
<tbody>
<tr>
<td>QLX</td>
<td>--</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SZB</td>
<td>--</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HJT</td>
<td>--</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GPW</td>
<td>--</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DLH</td>
<td>--</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>XCP</td>
<td>75</td>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NDJ</td>
<td>28</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FXB</td>
<td>194</td>
<td>36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>JCN</td>
<td>20</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BGQ</td>
<td>167</td>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KMC</td>
<td>180</td>
<td>36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RXT</td>
<td>82</td>
<td>18</td>
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<td></td>
</tr>
<tr>
<td>KFN</td>
<td>47</td>
<td>9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
APPENDIX K: OBJECT LOCATION MEMORY

Stimulus # 1 – Subjects are asked to study for one minute.

Stimulus # 2 – Subjects are asked to cross out items that have changed places.

Total Number Correct: _________
APPENDIX L: EXAMPLE FROM BOSTON NAMING TEST

"Comb"  "House"  "Toothbrush"

Boston Naming Test

ID: __________

1) Number of Correct Responses (No Cues): ________/60

2) Number of Stimulus Cues Required: ________/60

3) Number of Correct Responses (w/ Stimulus Cue): ________/60

4) Number of Phonemic Cues Required: ________/60

5) Number of Correct Responses (w/ Phonemic Cue): ________/60

Total Score (Total 1 + Total 3): __________