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Steroid Hormones and Memory in Healthy Elderly Men, in Women Estrogen-Users and Non-users and in Patients with Alzheimer's Disease

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Abstract

Relationships between the steroid hormones estradiol (E_2), testosterone (T), cortisol (CRT) and dehydroepiandrosterone-sulfate (DHEAS), memory and mood were investigated in men, in women estrogen-users and non-users, and in patients with Alzheimer's Disease (AD). In Study 1, 72 year-old healthy men and women estrogen-users performed better than estrogen non-users on Forward and Total Digit Span, which test attention and short-term memory, concomitant with their higher E_2 levels. The estrogen-users performed better than the men and the non-users on Delayed Selective Reminding, a test of explicit verbal memory. Men and women with higher CRT levels performed worse on several explicit verbal memory tests compared to those with lower endogenous CRT levels. In Study 2, male patients with AD performed better than estrogen non-using women with AD on several everyday memory tests, and women estrogen-users with AD performed similarly to the men. Both the men and estrogen-users had higher levels of E_2 than the non-users. AD patients with higher endogenous levels of DHEAS performed better than those with lower levels on several everyday memory tests, and AD patients with higher CRT levels were impaired on one aspect of everyday spatial memory, Route Recall. In Study 3, no differences in hormone levels between AD patients and age-matched healthy elderly controls were found. The AD patients were most severely impaired on tasks involving explicit verbal recall compared to healthy controls , and least impaired on short-term memory and concentration tasks. The AD patients reported more dysphoric mood and mental dulling symptoms than healthy age-matched controls, but they did not report feeling less positive about the future. Taken together, these results suggest that higher levels of DHEAS and E_2 are related to better memory performance in both healthy elderly men and women and in patients with AD, and higher CRT levels are associated with poorer explicit verbal memory performance in healthy elderly men and women. Some of the specific morphological and biochemical actions of these hormones on brain sites important for memory are discussed as possible mechanisms of action for these hormonal effects, and future studies that might further clarify the role of these steroid hormones on memory are suggested.

Résumé

Nous avons étudié la relation qui existe entre les hormones stéroïdiennes estradiol (E_2), testostérone (T), cortisol (CRT) et déhydro-épiandrostérone (DHEAS) d'une part, et la mémoire et l'humeur d'autre part, chez des hommes et des femmes qui prennent de l'oestrogène et n'en prennent pas et chez des sujets atteints de la maladie d'Alzheimer (MA). Dans le cadre de l'étude 1, un groupe de sujets de 72 ans comprenant des hommes sains et des femmes recevant de l'oestrogène ont obtenu de meilleurs résultats que des femmes ne prenant pas d'oestrogène au test *Forward and Total Digit Span* (mesure de la concentration et de la mémoire à court terme), tout en présentant des taux plus élevés de E_2. Les femmes qui prenaient de l'oestrogène ont obtenu de meilleurs résultats que les hommes et que les femmes qui ne prenaient pas d'oestrogène au test *Delayed Selective Reminding*, qui mesure la mémoire verbale explicite. Les hommes et les femmes qui présentaient des taux plus élevés de CRT ont obtenu de moins bons résultats que les sujets présentant des niveaux de CRT endogène moins élevés à plusieurs tests de mémoire verbale explicite. Dans le cadre de l'étude 2, les sujets masculins atteints de MA ont obtenu de meilleurs résultats à plusieurs tests de mémoire courante que les femmes qui ne prenaient pas d'oestrogène et qui souffraient de MA; les femmes atteintes de MA qui prenaient de l'oestrogène ont obtenu des résultats comparables à ceux des hommes. Les hommes ainsi que les femmes qui prenaient de l'oestrogène présentaient des taux de E_2 plus élevés que les femmes qui ne prenaient pas d'oestrogène. Les patients atteints de MA qui présentaient des taux plus élevés de DHEAS endogène ont obtenu de meilleurs résultats à plusieurs tests de mémoire courante que les patients chez qui ces taux étaient plus bas; les patients atteints de MA qui présentaient des taux de CRT plus élevés ont obtenu de moins bons résultats en ce qui a trait à un aspect de la mémoire spatiale courante (*Route Recall*). Dans le cadre de l'étude 3, aucune différence n'a été observée entre les patients atteints de MA et les sujets sains de même âge pour ce qui est des taux d'hormones. C'est au chapitre des tâches d'évocation verbale explicite que les patients atteints de MA étaient le plus désavantagés par rapport aux sujets témoins sains, et au chapitre des tâches de mémoire à court terme et de concentration qu'ils l'étaient le moins. Les sujets atteints de MA se plaignaient davantage d'états dysphoriques et de symptômes d'atténuation des facultés mentales que les sujets témoins de même âge, sans pour autant se montrer moins optimistes face à l'avenir. Dans l'ensemble, ces résultats semblent indiquer que les niveaux plus élevés de DHEAS et de E_2 sont liés à un meilleur fonctionnement de la mémoire tant chez les hommes et les femmes âgés sains que chez les patients atteints de MA, et qu'il existe un lien entre des taux de CRT plus élevés et la détérioration de la mémoire verbale explicite chez les hommes et les femmes âgés sains. L'auteur analyse certains effets morphologiques et biochimiques spécifiques qui visent certains sites cérébraux importants pour la mémoire et pourraient donc constituer le mode d'action de ces hormones; enfin, il propose différentes études qui pourraient contribuer à préciser le rôle de ces hormones stéroïdiennes dans la mémoire.

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sincerely hope that this may be the case.

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Statement of Original Contribution

In the past, reports have been made concerning the relationships between estrogen and memory in naturally cycling, surgically menopausal and postmenopausal women, and in young men. However, no investigation had looked at estrogen in both elderly women and men at the same time with an extensive test battery. Similarly, testosterone levels and memory had been investigated in men, but not in elderly women and men together, and an extensive memory battery had not previously been utilized in conjunction with hormonal assays in these populations. Dehydroepiandrosterone sulfate (DHEAS) levels and their relation to memory had never been investigated with a large battery of standardized cognitive tests in elderly men and women. Cortisol (CRT) levels had been investigated over time in healthy elderly men and women, but not in conjunction with DHEAS levels. Thus, the inclusion of both elderly men and women estrogen-uses and non-users in study 1, and the measurement of four steroid hormones represents a first in the literature. This is an important contribution because it allows direct comparisons between hormones and cognition in men and women and may help to clarify the relationships that contribute to gender differences in cognitive aging.

Study 1 represents the first attempt to investigate relationships between four steroid hormones and aspects of cognitive behaviour in the same sample. Although longitudinal studies of cognition have been reported, there has never been an account of the relationships between the changes in both memory performance and these four steroid hormones in elderly men and women. This longitudinal study avoids some of

the problems encountered in cross-sectional studies of aging that have to consider cohort effects on cognitive tasks and hormone levels.

Another innovative aspect to this work was the use of a battery of ecologically valid everyday memory tests. This allowed for investigation of the relationships between everyday memory performance and hormone levels, as well as validity comparisons between performance on everyday memory tests and more traditional neuropsychological tests. This ecologically valid test battery had not been used before in such a large healthy elderly sample. Nor had it been fully administered to patients with Alzheimer's Disease (AD), or been validated against such a comprehensive memory test battery.

In Study 2, a relatively large sample of AD patients were recruited, levels of the same four steroid hormones were measured and everyday memory tests were administered. The results indicated a role for endogenous DHEAS in memory function that had been speculated upon but never before reported in AD patients, and provided further support for possible roles for CRT and E_2 in the memory deficits of AD as well, adding to the very preliminary existing research base.

Study 3 helped to clarify the endocrinological differences between healthy elderly controls and AD patients. Whereas it had been controversial in the literature whether DHEAS, CRT and/or estradiol (E_2) levels differed between AD patients and controls, this study found no such differences in a large sample. Comparisons between the AD patients and the controls on the everyday memory tests provided some insight regarding the types and severity of everyday memory deficits in AD and spoke to the

question of how the cognitive pathology in AD is different from normal aging. Additionally, item and factor analysis of the Geriatric Depression Scale revealed new information regarding the type of depressive symptomatology associated with AD compared to healthy age-matched control men and women.

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List of Abbreviations

ACh	Acetylcholine
ACTH	Adrenocorticotropic Hormone
AD	Alzheimer's Disease
ADX	Adrenalextomized
AR	Androgen Receptor
BDI	Beck Depression Inventory
BSO	Bilateral Salpingo-oophorectomy
CAH	Congenital Adrenal Hyperplasia
CDR	Clinical Dementia Rating
CEE	Conjugated Equine Estrogen
ChAT	Choline Acetyltransferase
CRH	Corticotropin Releasing Hormone
CRT	Cortisol
CT	Computerized Tomography
DES	Diethylstilbestrol
DEX	Dexamethasone
DHEA	Dehydroepiandrosterone
DHEAS	Dehydroepiandrosterone-sulfate
DNA	Deoxyribonucleic acid
E_1	Estrone
E_2	Estradiol
ER	Estrogen Receptor
ERT	Estrogen Replacement Therapy
FM	Female to Male transsexual
GABA	gamma-aminobutyric acid
GnRH	Gonadotropin Releasing Hormone
GDS	Geriatric Depression Scale
GR	Glucocorticoid Receptor
HACU	High-affinity Choline Uptake
HPA	Hypothalamic-Pituitary-Adrenal
HPG	Hypothalamic-Pituitary-Gonadal
LTP	Long-term Potentiation
MAACL-R	Multiple Affect Adjective Checklist-Revised
MAO	Monoamine Oxidase
MF	Male to Female transsexual
MMSE	Mini Mental Status Examination
MPA	Medroxyprogesterone Acetate
MR	Mineralcorticosteroid Receptor
MRI	Magnetic Resonance Imaging
mRNA	messenger Ribonucleic Acid
NFT	Neurofibrillary Tangles
OVX	Ovariectomized

PET	Positron Emission Tomography
POMS	Profile of Mood States
RIA	Radioimmunoassay
RBMT	Rivermead Behavioral Memory Test
RNA	Ribonucleic Acid
SP	Senile Plaques
SRT	Selective Reminding Test
Ss	Subjects
T	Testosterone
T1	Time 1
T2	Time 2
TAH	Total Abdominal Hysterectomy
WMS	Wechsler Memory Scale
WMS-R	Wechsler Memory Scale-Revised

Steroid Hormones and Memory in Healthy Elderly Men, in Women Estrogen-users and Non-users, and in Patients with Alzhiemer's Disease

Introduction

One of the most pervasive sequela of aging in humans is memory loss. As the Canadian population grows increasingly older, understanding memory functioning in normal aging as well as the more severe memory impairments that occur with Alzheimer's Disease (AD) is becoming an increasingly important scientific endeavor. This dissertation reports on several investigations of the relationships between different steroid hormones and aspects of memory in both normal aging and in AD. In addition to investigating both healthy elderly and AD populations, this dissertation is unique in that it investigated both men and women, and assessed, in the same individuals, four different steroid hormones that have been linked to cognitive functions.

In order to understand the rationale behind these studies, it is necessary first to review the literature in a number of different areas. First, different types of memory are described, and the changes in various memory systems that occur with aging are reviewed along with age-related changes in the production of the steroid hormones of interest. The general neurobiology of memory is discussed, and the specific effects that each hormone has on memory systems in the brain are analyzed, followed by a review of behavioral studies linking each hormone to memory in both animals and humans. The aging process in the brain during healthy aging is compared to the process that occurs in AD, and the behavioral and clinical profile of AD is described, followed by a review of studies linking each hormone to memory functioning in AD.

Specific instruments that are used for assessing memory in aging and the need for ecologically valid memory tests are reviewed, and finally, the general neurobiology of mood and the effects of each hormone on mood are outlined.

Memory, Aging and Hormones

Memory Systems:

In its broadest sense, cognition refers to the process of knowing, and encompasses the domains of thinking, reasoning, decision making, problem solving, categorizing, remembering and imagining. Indeed, it refers to all the higher intellectual processes. The focus of these experiments is on memory, a critical component of cognition which encompasses everything we have recently perceived and everything that we know. It generally includes the processes of acquisition, retention and retrieval, but historically its components have been classified in a variety of ways by different investigators.

Tulving (1983), for example, divides memory into three distinct subsystems: procedural, semantic and episodic. Procedural memory describes learned habits, both motor and cognitive, such as brushing one's teeth, remembering how to tie a shoelace or how to carry on a conversation. Semantic memory is more representational in nature, dealing with memory for names of objects and other non-contextual items, while episodic memory is the system that deals with specific events, detailing the time and place of occurrence. These systems are concentrically embedded, with procedural memory as the most general, semantic memory as a subset of procedural memory, and finally episodic memory as a more specific subset of semantic memory.

Other theorists suggested different ways of classifying memory. Craik (1991) conceptualized memory in terms of memory processes, making the distinction between short-term (primary) memory, material that has just been presented or recalled and is thus "in mind", and long-term (secondary) memory, material which has left conscious awareness. Primary memory is best measured by the recency effect in free recall and the digit span test (Craik, 1991), whereas secondary (long-term) memory is assessed by any task in which material that has left conscious awareness is recalled. Thus, the distinguishing factor between primary (short-term) and secondary (long-term) memory is whether an item is held "in mind" or not, rather than the duration of time before recall.

A component of primary memory that has received much recent research attention is working memory, first introduced by Baddeley and Hitch (1974). Working memory describes tasks in which information must be held in mind at the same time as some other task, such as computation or decision making, is being carried out on that or other material. Working memory is an essential element of other functions, such as encoding for primary memory, problem solving and complex decision making.

An important type of secondary memory is *prospective memory*, referring to situations in which a person must remember to carry out some task in the future. Essentially, prospective memory tasks involve remembering to remember, for example remembering to call someone tomorrow or to stop by the grocery store on the way home. These tasks are often difficult as they provide few cues to remind the individual of the task (Craik, 1994). Although this appears to be an important aspect

of memory, there has been relatively little work on this topic.

Memory tasks have also been divided into those assessing *explicit* vs. *implicit* memory (Craik, 1991), a distinction that has also been referred to as *declarative* vs. *non-declarative* (Squire & Zola-Morgan, 1991). Tests during which the individual is aware that their memory is being tested measure explicit memory. Tests of implicit memory, measuring incidental memory for things that the individual was unaware that they were supposed to be learning, have shown that prior experience can affect later performance in the absence of conscious knowledge or conscious recollection of the original episode (e.g. Schacter, 1987; Tulving, Schacter & Stark, 1982), an effect that is known as *priming*.

Particularly in the sex differences literature, a distinction has also been drawn between verbal and visual/spatial skills (for review, see Hampson & Kimura, 1992). Verbal skills include spelling, speech acquisition, verbal articulation and verbal fluency, whereas visual/spatial skills encompass spatial orientation, spatial visualization and flexibility of closure. There is a gender difference in performance on these tasks such that men generally outperform women on tests of visual/spatial functions such as mental rotations, whereas women are generally superior on verbal tasks such as verbal articulation and verbal fluency (Jarvick, 1975). Whether or not this gender difference in cognitive performance also holds for verbal versus visual/spatial *memory* tasks is unclear, as no gender differences are reported in the norms of standardized memory tests that include both verbal and visual/spatial subtests (e.g. Wechsler Memory Scale-Revised; Wechsler, 1987). However, some studies have shown that women outperform

men on short-term verbal memory tasks (Hampson & Kimura, 1992).

Changes in memory with normal aging:

The belief that memory functions decline with aging is commonly held in our society. Although there is some justification for this contention based on subjective and objective studies, not all memory functions decline with age, and those that do decline do so to different degrees (for recent reviews see Craik, 1991, 1994; Craik & Jennings, 1992; Kausler, 1994; Smith, 1996). The largest performance differences between young and older adults are found on explicit memory tasks requiring recall of recently presented word lists or passages (Craik, 1994). These differences are largest in free recall of recently presented material, are less in cued recall, and are less again in recognition memory. Older adults also show decrements in tasks assessing working memory in terms of both speed and accuracy (Dobbs & Rule, 1989), and show declines in memory for source (episodic memory) relative to younger adults (McIntyre & Craik, 1987). However, in tasks such as Forward Digit Span and in memory for well-learned knowledge, age differences in performance are slight or non-existent (Craik, 1991), indicating that short-term, semantic and procedural memory remain relatively intact. Similarly, most (Light & Singh, 1987) but not all (Kausler, 1994) studies of implicit memory failed to find age differences. Moreover, when age differences in implicit memory did occur, they were of a considerably reduced magnitude than age differences on working memory and free recall (Smith, 1996).

There are also some gender differences in the types of memory changes that occur with aging. Women showed significantly less age-related decline in verbal

memory than men, whereas men had better preservation of visuospatial abilities, as measured with visuoconceptual, constructional and spatial memory tasks (West, Crook & Barron, 1992). Scores of men on the Selective Reminding Test, WMS Visual Reproduction, the Mini-Mental Status Exam and on items from the Blessed Information-Memory-Concentration test declined more rapidly with age than those of women (Wiederholt et al., 1993), supporting the idea that women maintain some memory functions better than men as they age.

Overall, tasks that assess visuospatial skills appear to show more detriments with advancing age than do those that are more verbal, such as naming ability and vocabulary (Albert, 1988). The particular tasks identified by Ardila & Rosselli (1989) as comprising a "factor G for aging" included the WAIS Block Design, Digit Symbol, Rey-Osterrieth Complex Figure and Porteus Mazes, all visuospatially oriented tasks.

Changes in steroid hormone levels with aging:

The major goal of the research described in this doctoral dissertation was to investigate the possible influence of changing levels of steroid hormones that occur with aging on memory in older individuals. Specifically, four steroid hormones known to influence both brain function as well as memory were studied - estradiol (E_2), testosterone (T), cortisol (CRT) and dehydroepiandrosterone-sulfate (DHEAS). Not only do these four steroid hormones influence brain areas critical for memory, as will be reviewed below, but they also influence different aspects of memory in both animals and humans. Furthermore, age-related changes occur in the endogenous production of some of these hormones.

Estradiol (E_2):

E_2 is the primary estrogen produced by the ovary. In premenopausal women, ovarian E_2 secretion accounts for 95% of the total E_2 that enters the circulation (Longcope, 1994). Estrone (E_1), a much weaker estrogen, is derived principally from the metabolism of E_2 and from the conversion of androstenedione, an androgen secreted by the adrenal gland (Levrant & Barnes, 1994). Around the age of 40 years, the ovary begins to decrease in size due to loss of follicles and changes in supporting tissues and cells, which, when coupled with subtle dysregulation of the hypothalamic-pituitary-gonadal (HPG) axis, results in the menopause at about age 51 (Longcope, 1994). The menopausal transition, the time between the onset of irregular monthly flow to the complete cessation of menstruation, takes an average of four years (Burger, 1996). After the menopause, virtually no E_2 is produced by the ovary, leaving only small amounts of E_1 as the primary source of estrogen in postmenopausal women. In fact, the ovarian secretion rate of both E_2 and E_1 decrease to negligible levels within 24 months of the last menses (Longcope, 1986).

This sharp decrease in estrogens available to the female brain after the menopause contrasts distinctly with the situation in males, who show only a very small decrease in estrogens over time (Simon, Preziosi, Barrett-Connor, Roger, Saint-Paul, Nahoul, & Papoz, 1992). Fully 80% of plasma E_2 in men arises from peripheral conversion of androgens to estrogens, while the other 20% is derived from testicular production (Braunstein, 1986). Although androgen levels decrease with increasing age in men (Tenover, 1996), production never ceases entirely, so that the precursor to E_2

is available in the brains of men lifelong. The normal male range of E_2 levels (37-220 pmol/L) overlaps with levels seen in the early follicular phase of regularly cycling women (110-440 pmol/L), and is generally higher than levels in postmenopausal women (<100 pmol/L; Department of Clinical Chemistry - Endocrine Norms, Jewish General Hospital, Montreal). Thus, it is clear that in older populations, males have greater exposure to estrogens than females, in contrast to the situation in younger adults where females have much higher average levels of estrogens than males.

Testosterone (T):

In women, both the adrenal and the ovary synthesize and secrete androgens. The ovary produces approximately 25% of total T production, while the adrenal produces a further 25% of circulating T. The remaining 50% of circulating T arises through peripheral conversion (Longcope, 1986). The menopause is associated with a decrease in ovarian androgen secretion and results in a decline in circulating T in most postmenopausal women (Longcope, 1994). In men, over 95% of circulating T is secreted by the testicular Leydig cells, while the remaining 5% is produced by the adrenals (Braunstein, 1986). Although there has not been universal agreement in the literature, 21 of 25 papers published between 1980 and 1993 have supported an age-associated decrease in male T levels (Tenover, 1996). Thus, with aging, T levels decline in both men and women.

Dehydroepiandrosterone-Sulfate (DHEAS):

In both men and women, DHEAS is derived almost exclusively from the adrenal gland and shows tremendous variation throughout the lifespan and between

individuals. On average, adrenal secretion of DHEAS is very high in the fetus, drops sharply after birth and remains low throughout childhood until the time of the adrenarche, when levels rise and once again reach high values in young adulthood (Hornsby, 1995). After the age of approximately 25 years, DHEAS levels drop an average of 2% per year, with the net effect at age 80 of levels about 20% of what they were at age 25 (Vermeulen, 1995). The overlap in values between men and women is significant, but men have levels of DHEAS that are about 10-30% higher, on average, than those of women (Vermeulen, 1995). In women, the decrease in DHEAS does not appear to be directly related to the endocrine events of the menopause, for there is no evidence that the menopause itself is characterized by any perturbation of adrenal steroid secretion (Longcope, 1994).

Cortisol (CRT):

In both men and women, CRT production usually remains stable with increasing age (Sharma et al., 1989; Sherman, Wysham & Pfohl, 1985; Waltman, Blackman, Chrousos, Riemann & Harman, 1991), which is consistent with the notion that the adrenals are not affected by the menopausal transition (Longcope, 1994). However, in some individuals CRT levels increase with aging, and it has been suggested that these individuals may be at an increased risk for cognitive impairments compared to others whose CRT levels do not change over time (Lupien et al., 1994; Lupien et al., 1995).

Neurobiology of Memory

Brain areas involved in learning & memory:

Over the past few decades, research has delineated not only the specific sites in the brain that are important for memory, but also the specialized memory functions that are subserved by these anatomical sites. Milner (1966) proposed that memory depends on the integrity of the medial temporal lobe, based on observations of the patient H.M. who had medial temporal lobe lesions accompanied by severe amnesia. The medial temporal lobe contains several anatomical structures including the hippocampus, the nearby subiculum and dentate gyrus, the amygdala, and the adjacent entorhinal, perirhinal, and parahippocampal cortex. The hippocampus itself is composed of three fields, the CA1, CA2 and CA3 areas.

Subsequent studies of brain lesions in humans, in non-human primates and in rats have examined the amnesia caused by lesions that encompass different structures within the medial temporal lobe in an attempt to localize the sites critical for memory functions (Squire, 1992). The narrowest type of lesion, caused in humans and animals by ischemia, damages the neurons in only the CA1 layer of the hippocampus. The next broadest type, termed an H lesion, encompasses the entire hippocampus plus the dentate gyrus and subiculum. An H+ lesion also encompasses the surrounding entorhinal cortex and the parahippocampal gyrus. Of the next largest lesions, the H+A+ lesion additionally subsumes the amygdala and underlying cortex, while the H++ lesion affects similar areas as the H+A+, but leaves the amygdala intact. By comparing memory performance of groups of subjects with differing degrees of neuronal damage in the medial temporal lobes, researchers have been able to identify the structures that are integral for different memory functions.

Humans with ischemic lesions showed moderately severe memory impairment compared to matched controls (Zola-Morgan, Squire, & Amaral, 1986). Ischemic monkeys also showed memory impairment compared to intact monkeys, and were just as impaired as H lesioned monkeys, indicating that the CA1 layer of the hippocampus is crucial for memory (Alvarez-Royo, Clower, Zola-Morgan & Squire, 1991). In comparison, both H lesioned and ischemic monkeys were less impaired than monkeys with H+ and H++ lesions (Alvarez, Zola-Morgan & Squire, 1995; Squire & Zola-Morgan, 1991), demonstrating that the surrounding cortical structures also play a role in memory functioning. Finally, no differences in memory performance were observed between H+A+ lesioned monkeys and H++ lesioned animals, suggesting that the amygdala does not play an important role in memory.

Having established the structures that are important for normal memory functions, work proceeded on the specification of the particular type of memory that is affected by damage to the hippocampus and surrounding cortex. The tasks most vulnerable to hippocampal damage all measure what has variously been termed *explicit, declarative, relational* or *configural* memory. This type of memory is distinguishable from *implicit, nondeclarative, procedural* or *habit* memory (Squire, 1992). The key elements of explicit memory are purposefulness accompanied by a feeling of familiarity about the past. Recall and recognition, the most commonly used tests of explicit memory, show the most impairment in hippocampal lesioned animals and humans, and are also the most impaired in normal aging (Craik & Jennings, 1992).

It has also been postulated that the hippocampus functions as a device for

forming new associates and conjunctions between previously unrelated events (Squire, Shimamura & Amaral, 1989), which is thought to be the process underlying declarative memory. The hippocampus is well suited for such tasks, as it is an active site of neural plasticity through the process of long-term potentiation (LTP; Gustaffson & Wigstrom, 1988). LTP is a rapid-developing and long lasting form of neural plasticity, which provides a mechanism for forming and storing conjunctions in the hippocampus. Such a high degree of neural plasticity could allow the hippocampus to accomplish the memory tasks of acquiring information about relationships and combinations among stimuli such that the resulting representation is flexible and accessible to multiple response systems (Zola-Morgan & Squire, 1993).

Implicit or nondeclarative memory includes tasks such as skillful behaviour or habits (procedural memory), which may encompass perceptuo-motor, perceptual and cognitive skills, as well as simple conditioning, including emotional learning, and the phenomenon of priming. Different brain systems appear to underlie these types of learning since lesions to the hippocampal regions leave these functions intact (Squire & Frembach, 1990; Moscovitch, Winocur & McGachlan, 1986; Musen, Shimamura & Squire, 1990). Some types of priming appear to be dependant on early-stage processing systems in the posterior neocortex (Squire, 1992).

The hippocampus plays only a temporary role in memory storage, and after a certain period of time it is not necessary for storage, recollection and manipulation of memories (Squire, 1992). This is demonstrated by studies of retrograde amnesia, which often occurs with hippocampal lesions, and is usually temporally graded, with

the most severe amnesia found for more recent events and less amnesia for more remote events (e.g. Kritchevsky & Squire, 1989). The severity of the lesion dictates the timespan of the amnesia, with smaller lesions resulting in amnesia for the near past, and larger lesions leading to amnesia for the past decade or more (e.g. Squire, Slater & Chace, 1975; Kopelman, 1989). Thus, neuropsychologists have concluded that the hippocampus works by gradually reorganizing and consolidating material in declarative memory, and after a certain amount of time has passed, the contribution of the hippocampus and adjacent structures diminishes and the neocortex alone gradually becomes capable of supporting usable permanent memory (Zola-Morgan & Squire, 1990; Milner, 1989; Squire, Shianmura & Amaral, 1989).

Neurotransmitter systems involved in learning and memory:

In addition to the anatomical importance of the hippocampus and adjacent cortical areas, certain neurotransmitter systems are critical for learning and memory. The cholinergic system has been associated with learning and memory functions in both humans and non-humans as evidenced by a large number of pharmacological, behavioral, and anatomical studies (for review see Gibbs, 1994). For example, in humans, administration of the cholinergic muscarinic receptor antagonist scopolamine produced learning and memory deficits for recent events (Drachman, 1977). In young adult monkeys scopolamine administration produced progressively more severe memory deficits as delay intervals were lengthened, similar to those observed in aged monkeys (Aigner, Walker & Mishkin, 1991).

A role for cholinergic processes in age related cognitive decline and in the

dementia of Alzheimer's Disease (AD) has been outlined as the "cholinergic hypothesis of geriatric memory dysfunction" (Bartus, Dean, Beer & Lippa, 1982). There is a great deal of evidence that the cholinergic system functions poorly in people with AD. A decrease in choline acetyltransferase (ChAT), the synthetic enzyme for acetylcholine (ACh), has been found in the brains of AD patients, particularly in the hippocampus (Reviewed by Perry, 1986). Reduced activity of acetylcholinesterase (AChE), the ACh degradation enzyme, was found in the cortex of AD patients over 30 years ago (Pope, Hess & Levin, 1965), but the significance of this finding was not appreciated until much later (reviewed by Hohmann, Antuono & Coyle, 1988). Other markers of cholinergic dysfunction found in AD patients include decreased amounts of endogenous ACh, impaired synthesis of ACh in vitro and decreases in high-affinity choline uptake (HACU; Rossor, 1988). A decrease in the number of cholinergic neurons of greater than 75% in the nucleus basalis of Meynert of the basal forebrain in postmortem AD brains was first documented by Whitehouse et al. (1982), and has since been confirmed on numerous occasions in both aging humans and animals (Gibbs, 1994).

Further evidence that the cholinergic system is critical for learning and memory comes from treatment studies in which small but significant improvements in learning and memory performance in aged monkeys and in humans with AD were found after treatment with AChE inhibitors such as tacrine (Bartus, Dean & Beer, 1983; Kumar & Calache, 1991). In some animal studies, transplantation of cholinergic neurons directly into the hippocampal formation led to functional recovery that was correlated

with the degree of cholinergic reinnervation of target tissues (Dunnett, Low, Iversen, Stenevi & Bjorklund, 1982; Danlioff, Bodony, Low & Wells, 1985). This suggests that cholinergic reinnervation of the hippocampal formation and cortex was primarily responsible for the functional recovery produced (Gibbs, 1994).

Other neurotransmitter systems have also been implicated in cognitive functioning but their effects on specific aspects of cognition have not been very well defined. Norepinephrine may be an important factor for attentional processes (McEntee & Crook, 1990) as well as for learning new associations (Frith, Dowdy, Ferrier & Crow, 1985) and memory retention (McGaugh, Liang, Bennett & Sternberg, 1984). Indeed, reduced concentrations of norepinephrine have been detected in the neocortex and hippocampus of AD brains (Rosser, 1988). Serotonin may play an inhibitory role in learning and memory such that higher levels of serotonin are detrimental to learning while lower levels facilitate learning (McEntee & Crook, 1991). gamma-aminobutyric acid (GABA) also appears to play a role in learning and memory, since GABA antagonists facilitated LTP in the hippocampus, a process thought to be critical for learning and memory (Wigstrom & Gustaffson, 1985). Additionally, excessive GABA activity in the brain caused by chronic use of benzodiazepines caused cerebral atrophy in humans (Moodley, Golomboc, Shine & Lader, 1993). Indeed, administration of a benzodiazepine antagonist prolonged the lifespan and improved memory in rats (Marczynski, Artwolh & Marczynska, 1994), leading the authors to propose a GABA/benzodiazepine theory of brain aging.

Steroid Hormones and Memory Systems in the Brain

Estrogen:

Estrogen Receptor Localization in the Brain:

Receptors specific for estrogen have been found in many brain areas, including the hypothalamus, pituitary, amygdala, caudate putamen, nucleus accumbens, substantia nigra, cingulate cortex, locus coeruleus, midbrain raphe nuclei, the basal forebrain and hippocampus (McEwen, Gould, Orchinik, Weiland & Wooley, 1996). The latter two structures have been associated with learning and memory, as previously described. Using autoradiographic techniques, estrogen receptors (ER) have been localized within the hippocampus primarily to the CA1 layer, but are also found to a lesser extent in the CA3 region and the dentate gyrus (Loy, Gerlach & McEwen,1988).

The primary action of steroid hormones in the brain seems to be through the alteration of the expression of specific genes or gene networks (Yammamoto, 1985). Hormonal influence on gene expression in many systems appears to occur at the DNA or transcriptional level, and the measurement of neurons expressing ER messenger ribonucleic acid (mRNA) accurately reflects this activity (Simerly, Chang, Muramatsu & Swanson, 1990). Therefore, much current research has focussed on the detection of steroid receptor mRNA, using *in situ* hybridization. The strongest hippocampal signal intensity of ER mRNA was found in the pyramidal layer of the subiculum and the presubiculum, with lower concentrations in the CA1, CA2 and CA3 pyramidal layers of the hippocampus and in the dentate gyrus (Simerly et al., 1990). ER mRNA was expressed in 80% or more of hippocampal neurons from both men and women in a postmortem study of human hippocampi in which none of the subjects had a history

of brain disease (Tohgi, Utsugisawa, Yamagata, & Yoshimura, 1995). In comparison to younger brains, those over the age of 65 years showed age-related reductions in the percent of ER mRNA-expressing neurons in the CA1 layer of the hippocampus.

Estrogen effects on brain morphology:

Although the hippocampus loses many, but not all, of its E_2 receptors shortly after birth, significant activational effects of estrogen on axonal growth, connectivity and function nonetheless occur in adults (Gould, Wooley, Frankfurt & McEwen, 1990; Weiland, 1992). Estrogen has been shown to increase synaptogenesis in the hippocampus. Following ovariectomy, female rats show a decrease in dendritic spine density in the CA1 layer of the hippocampus, which is reversed when estrogen is administered after the surgery (Gould et al, 1990). This effect of estrogen on the density of dendritic spines on hippocampal neurons is also evident *in vivo* during various phases of the estrous cycle of normal female rats. Dendritic spine density in the CA1 hippocampal layer increased and then decreased over the 72 hour period between proestrus and estrous, mirroring the changes in E_2 levels that occur over this time period (Wooley & McEwen, 1992). Estrogen also affects neuronal sprouting after hippocampal lesions in female rats. Sprouting was decreased in OVX rats compared to intact females, but was restored to intact levels by subsequent administration of estrogen. In males, castration did not affect successive hippocampal dendritic sprouting (Scheff, Morse & DeKostky, 1988a).

In a recent *in vitro* study of rat hippocampal neurons, cells exposed to beta-E_2 for three days showed a twofold increase in dendritic spine density which was not seen

in cells treated with alpha-E_2 or progesterone (P). In neurons cultured with a combination of E_2 and P treatment, spine density decreased somewhat from baseline, indicating that the P completely blocked the tropic effects of E_2 treatment (Murphy & Segal, 1996). Also, the effect of E_2 on hippocampal spine density was blocked by an N-methyl-D-aspartate (NMDA) receptor antagonist, suggesting that E_2 works to enhance hippocampal LTP, and thus memory function, through activation of the NMDA receptor. Similarly, E_2 enhanced the sensitivity of the hippocampus to glutamate activation by increasing NMDA glutamate binding sites and the density of agonist sites by 30% in the CA1 region of the hippocampus in OVX rats (Weiland, 1992). These findings suggest that E_2 may be acting on the hippocampus through direct effects on NMDA receptors.

Estrogen effects on neurotransmitters:

The cholinergic system has been associated with learning and memory functions in both humans and non-human animals (Bartus et al., 1982). ChAT, the enzyme needed to synthesize acetylcholine, is directly affected by estrogen. The administration of estrogen to OVX rats increased ChAT activity in the frontal cortex and the CA1 layer of the hippocampus (Luine, 1985). However, this did not occur when estrogen was administered to male rats. In female rats, estrogen counteracted the detrimental effects of scopolamine, a cholinergic muscarinic antagonist, on T-maze performance (Dohanich, Fader & Javorsky, 1994). In OVX rats, levels of high-affinity choline uptake (HACU) in both the frontal cortex and hippocampus and ChAT activity in the hippocampus decreased by 5 weeks post-OVX (Singh, Meyer, Millard & Simpkins,

1994), and were restored to preoperative levels following 5 weeks of estrogen replacement. The mechanism by which estrogen up-regulates the expression of ChAT in females may be through direct tropic effects on cholinergic neurons in the basal forebrain, through increasing the sensitivity of cholinergic neurons to growth factors, or via both mechanisms (Toran-Allerand et al., 1992).

Estrogen also acts on the nigrostriatal and mesolimbic dopaminergic systems, and can have both pro- and anti-dopaminergic actions depending on the dose and duration of the treatment. Although not directly implicated in memory, these actions have possible effects on both normal and abnormal locomotion (McEwen, Alves, Bulloch & Weiland, 1996). Estrogens also influence the serotonergic system in the rat hippocampus and forebrain. Female rats had a greater synthesis and turnover of 5-hydroxytryptamine in the hippocampus than males (Haleem, Kennett & Curzon, 1989), indicating a higher serotonin metabolism. Estrogen caused decreased levels of monoamine oxidase (MAO), the enzyme that degrades norepinepherine, dopamine and serotonin, in the amygdala and hypothalamus of OVX rats (Luine, Khylchevskaya & McEwen, 1975), and also led to increased norepinepherine synthesis in these same regions (Greengrass & Tonge, 1974). Thus, if norepinepherine does play a role in learning and memory as has been suggested (Frith et al., 1985; McGaugh et al., 1984), E_2 may also enhance memory via this mechanism.

It has been customary to distinguish between genomic and non-genomic steroid actions. Genomic effects are thought to occur at the level of gene transcription affecting neurotransmitter enzyme induction, synthesis of cellular products and

neuronal growth and morphology. Such effects are relatively long-lasting and have a delayed latency. The effects discussed above are primarily regarded as genomic. Non-genomic effects are those that occur more immediately and have direct effects on neuronal activity, which may be mediated by cell membrane receptors (McEwen, Krey and Luine, 1978; McEwen, 1991).

Non-genomic effects of estrogens vary widely throughout the brain. Administration of estrogen to intact female rats resulted in increased electrical activity in the hippocampus during the estrous phase of the cycle, when endogenous estrogen levels are low (Butcher, Collins & Fugo, 1974), and increased the triggering and amplitude of excitatory post-synaptic potentials in CA1 hippocampal slices (Wong & Moss, 1991; Wong & Moss, 1992). E_2 administration also increased spike amplitude in the CA1 layer of hippocampal slices from male rats (Teyler, Vardaris, Lewis & Rawitch, 1980). Other E_2 actions defy such classification, leading researchers to question the distinction between genomic and non-genomic mechanisms. For example, cell surface receptors may signal changes in gene expression, while genomic actions sometimes affect neuronal excitability, often quite rapidly. As well, estrogens may operate in conjunction with neurotransmitters to produce effects, sometimes involving collaborations between groups of neurons (McEwen, 1994).

Taken together, the changes in neuroanatomy and neurochemistry induced by E_2 provide a basis for thinking that estrogen may play an important role in facilitating and sustaining specific cognitive functions in women, and may even influence the cognitive declines that occur with normal aging and the severe memory deficits in

individuals with AD. For males, however, the evidence concerning the enhancing effects of estrogens on brain morphology and neurochemistry is somewhat less clear.

Testosterone:

Testosterone receptor localization in the brain:

Autoradiographic studies show that specific receptors for T are found predominantly in the preoptic area of the hypothalamus, the amygdala, cortex and hippocampus of rats (McEwen, 1980). Using *in situ* hybridization to detect neurons in the rat brain that express androgen receptor (AR) mRNA, Simerly et al. (1990) found the strongest hippocampal signal intensity in the amygdala, septum, hypothalamus, brainstem, motor cortex and the hippocampus. In another *in situ* hybridization study 80% or more of the neurons in the CA1, CA2, CA3 and hilus regions of the hippocampus in humans contained mRNA for ARs (Toghi et al., 1995). Additionally, the ratio of mRNA-containing neuron density to total neuron density decreased significantly with age for ARs in the CA1 region (Toghi et al, 1995), indicating that ARs are present in brain areas critical for memory and that the density of functional ARs in these areas decreases with increasing age.

Effects of T on brain morphology and neurotransmitters:

T, during prenatal life, is responsible for many sex differences in the structure of male and female brains. These effects are discussed in a later section detailing sex differences in the brain caused by the hormonal environment.

Metabolism of T:

T is metabolized in the brain to E_2 via the enzyme aromatase. The question of

whether the effects of prenatal T exposure on the structure of certain brain areas is due to T itself, or if T is metabolized to E_2 which then affects development, has yet to be fully resolved. Researchers have investigated this question by looking at aromatase activity in the brains of several species at different time frames during development. Since aromatase must be present for T to be converted to E_2, and there must be ERs present in the brain area of question for E_2 to be effective, these two conditions have been investigated.

Not surprisingly, the highest concentrations of aromatase activity are found in the hypothalamus, preoptic area and the amygdala, areas involved in reproductive behaviour (Roselli, 1995). However, aromatase activity is also detectable in the cortex and hippocampus of neonatal monkeys (MacLusky, Clark, Naftolin, & Goldman-Rakic, 1987; Naftolin, 1994). In fact, ARs and ERs generally co-localize with aromatase in the brain (Naftolin, 1994), indicating that the brains of young monkeys are capable of converting T to E_2 in areas of the brain critical for learning and memory.

In male rats, accuracy in a radial arm maze was impaired by the administration of an aromatase inhibitor during early postnatal life (Williams & Meck, 1993). Neonatal castration led to a female-like pattern of Morris water maze performance, and E_2 administration to newborn female rats led to male-like water maze performance (Williams & Meck, 1991). These results suggested that the sexually dimorphic effects of T administration on brain structure and behaviour were due to its conversion to E_2 (Roof & Havens, 1992; Williams & Meck, 1991, 1993; McEwen et al, 1996).

Cortisol:

Cortisol receptor localization in the brain:

Glucocorticoid receptors in the rat brain have been categorized into two distinct systems: the classic glucocorticoid receptor (GR, type II), to which the potent synthetic glucocorticoid, dexamethasone (DEX) preferentially binds, and the type I receptor, which is biochemically similar to the mineralcorticosteroid receptor (MR; for review see McEwen & Gould, 1990). Corticosterone in the rat brain binds to both of these receptors. However, the GRs are more responsive to changing levels of glucocorticoids that regulate stress responses, whereas the MRs are saturated at normal low physiological concentration of glucocorticoids and do not respond to environmental stressors (McEwen et al., 1992). Thus, GRs are most commonly studied when investigating the effects of glucocorticoids in the brain and on behaviour. The highest levels of glucocorticoid binding have been found in the hippocampus, followed by the hypothalamus (Reul & deKloet, 1985).

GR mRNA was localized to the CA1, CA2 and dentate gyrus of the hippocampus, as well as the hypothalamus, thalamus, amygdala, brainstem and cerebellar cortex in an *in situ* hybridization study of the rat brain (Aronsson et al, 1988). A human postmortem study found GR mRNA expression in over 80% of hippocampal neurons, but this percentage decreased in the CA1, CA3 and the hilus with advancing age (Tohgi et al, 1995).

Effects of cortisol on brain morphology:

Exposure to high levels of glucocorticoids, either due to environmental stress or via exogenous administration, has been associated with a number of physiological

and biochemical actions in the brains of rodents, monkeys and humans, particularly in the hippocampus. Corticosterone, given in high doses over three weeks to intact rats produced a significant decrease in dendritic branchpoints of the apical dendritic tree of CA3 pyramidal neurons in the hippocampus (Wooley, Gould & McEwen, 1990). The exposure of rats to environmental stressors also resulted in decreases in long-term potentiation in the hippocampus (Foy, Stanton, Levine & Thompson, 1987).

In African green monkeys who suffered severe and prolonged abuse by cagemates, degeneration and depletion of hippocampal neurons in the CA1 and CA3 layers was found after death (Uno, Tarara, Else, Suleman & Sapolsky, 1989). CRT pellets implanted in the vicinity of the hippocampus in adult vervet monkeys induced degeneration of the CA3 pyramidal neurons and their dendritic branches (Sapolsky, Uno, Rebert & Finch, 1990). When DEX was administered to pregnant rhesus monkeys, degeneration and depletion of hippocampal pyramidal and dentate granular neurons occurred in the brains of the fetuses (Uno et al., 1990). The infant monkeys who were exposed to DEX *in utero* had higher levels of CRT at baseline and after exposure to stress at the age of 9 months, and hippocampal formations about 30% smaller than age-matched vehicle treated controls, as assessed by MRI (Uno et al., 1994). Taken together, these studies have provided strong evidence that high levels of glucocorticoids in both the adult and fetal money, whether endogenously or exogenously induced, cause severe damage to neurons, particularly the hippocampal pyramidal neurons in the CA layers.

In the human brain detrimental effects of elevated cortisol have also been

demonstrated. Patients with Cushing's Syndrome have CRT hypersecretion and lack the normal CRT circadian rhythm (Starkman, Gebarski, Berent & Schteingart, 1992). In an MRI study, 64% of Cushing's Syndrome patients had hippocampal formation volumes that were below those found in healthy controls, and their CRT levels were negatively correlated with hippocampal formation volume (Starkman et al., 1992). Patients with mood disorder and accompanying memory deficits also show elevated CRT levels (Sikes, Stoken, & Lasley, 1989).

Based on this and other research, Sapolsky, Krey and McEwen (1986) developed the "glucocorticoid cascade hypothesis" of stress and aging, which postulates that the hippocampus normally serves to inhibit glucocorticoid feedback to the HPA axis. With aging, exposure to extreme stressors or exogenous administration of glucocorticoids, degeneration appears in hippocampal neurons. This observed degeneration leads to a loss of sensitivity of the axis to feedback inhibition. Thus, the hippocampus fails to exert the appropriate inhibition to the HPA axis, so basal ACTH is secreted in high quantities, leading to hypersecretion of glucocorticoids from the adrenal. This hypersecretion leads to more degeneration of hippocampal neurons, further down-regulation of the number of receptors per neuron, and eventual neuronal death, finally resulting in further dysregulation of feedback inhibition (Sapolsky et al, 1986). This cascade of glucocorticoid hypersecretion, hippocampal damage, impaired negative feedback, sustained hypersecretion and further neuronal loss is postulated to have severe behavioural consequences, such as memory impairments, immunosuppression, osteoporosis, hyperglycemia, arteriosclerosis and steroid diabetes.

Thus, this model makes predictions of biological and behavioural outcomes associated with hypercortisolemia that can be experimentally tested.

DHEAS:

DHEAS localization in the brain:

DHEA and its sulfate, DHEAS, have been identified as the most prevalent steroid hormones in the brains of both rats and humans, where they are found at levels many times higher than those in the plasma (Majewska, 1995). DHEAS is the precursor of many other steroid hormones in the brain, including other androgens and estrogens. DHEA must first be converted to androstenedione by two catabolizing enzymes, 3-B-OH-dehydrogenase and delta$^{4-5}$ isomerase. Androstenedione, in turn, is converted to T via the enzyme 17 B-OH-dehydrogenase. T can then be converted to E_2 via aromatase. For these conversions to occur, the specific enzymes must be present to fuel the conversion (Speroff, Glass & Kase, 1989).

Postmortem studies have found the highest DHEAS concentrations in the pituitary, amygdala, hippocampus and hypothalamus in the brains of 3 men (aged 56, 59 and 75) and two postmenopausal women (Lanthier & Patwardhan, 1986), and in the temporal, prefrontal and parietal cortex and cerebellum of 9 elderly women and 1 elderly man (Lacroix et al., 1987). In most regions, the women had higher concentrations of DHEA and DHEAS than the men (Lanthier & Patwardhan, 1986). This is contrary to what is seen in plasma, where men have approximately 30% higher DHEAS levels than women (Vermeulen, 1995).

DHEAS effects on neurotransmitters and brain morphology:

At low concentrations DHEA and DHEAS function as allosteric antagonists of $GABA_A$ receptors, and this non-competitive binding inhibits GABA-induced neuronal activity (Majewska, Demirgoren, Spivak & London, 1990). The GABA agonist steroid THP administered to cultured fetal hippocampal tissue induced a reversible structural regression of neurons in this region, indicating that GABAergic steroids play a role in shaping the neuronal architecture in the hippocampus (Brinton, 1994). Thus, since DHEA and DHEAS have GABAergic antagonist properties, it might be expected that administration of these hormones would lead to neuronal growth in the hippocampus. Indeed, when low doses of DHEA and DHEAS were administered to 14 day embryonic mouse brain cultures, enhanced neuronal and glial survival was found (Roberts, Bologna, Flood & Smith, 1987). This suggests that DHEA and DHEAS may influence learning and memory processes through their GABAergic antagonistic properties in the hippocampus (Majewska, 1995).

DHEAS also has several fast-acting non-genomic effects in the hippocampus. Application of DHEAS increased population spike amplitudes and excitatory postsynaptic potential slopes in the CA1 field of the hippocampus, increased the firing rate of hippocampal principal cells and interneurons in male rats and attenuated GABA-mediated inhibition in the dentate gyrus and CA1 hippocampal layer (Steffensen, 1995). Intermediate doses of DHEAS administered to rats enhanced primed burst potentiation, resulting in a lasting increase in the amplitude of the CA1 population spike produced by minimal electrical stimulation (Diamond, Branch & Fleshner, 1996). Similarly, DHEAS increased the excitability of CA1 hippocampal

neurons in hippocampal slices from rat brains, an effect that occurred within minutes and was reversible (Meyer & Gruol, 1994). In intact rats, DHEAS application to the dentate gyrus resulted in increases in LTP at all doses in relation to baseline (Yoo, Harris & Dubrovsky, 1996). Taken together, these results indicate that DHEAS may influence synaptic transmission through multiple mechanisms, resulting in increased excitability of postsynaptic neurons.

DHEAS and Cortisol:

In animal models, DHEAS has antiglucocorticoid actions in the liver by blocking the enzymatic effects of glucocorticoids (Svec & Lopez-S, 1989; McIntosh & Berdanier, 1988). Svec & Lopez-S (1989) suggested that the ratio of DHEAS to CRT might serve as an appropriate measure of glucocorticoid agonist activity. If it is the case that AD patients have lower DHEAS than age-matched controls (Sunderland et al., 1989), they could conceivably have an agonist to antagonist ratio half that of the normal population, which could lead to a mild but progressive degenerative effect on hippocampal cells. If such degeneration caused dysregulation in feedback mechanisms to the adrenals (Sapolsky et al., 1986), progressive hippocampal damage, and presumably memory impairment, would occur.

Hormonally Induced Sex Differences in Brain Anatomy:

It is established that estrogen acts through the genome during critical periods of neonatal growth to promote sexual dimorphism in a variety of brain tissues, including but not limited to areas that control gonadal function and reproductive behavior (McEwen, 1991; 1994). The organizationally dimorphic patterns of neuronal

connectivity that develop in males and females consequent to differential neonatal hormonal exposure may be responsible for the sex differences in cognitive functions that are observed later in life. Differences in the anatomy of male and female brains provide indirect evidence in support of this view. Studies in rats have identified several brain areas that are anatomically different in the two sexes. Roof and Havens (1992) found that male rats showed more lateral asymmetry in the dentate gyrus granular cell layer of the hippocampus than did females. Moreover, when females were treated with T at postnatal days 3 and 5, their dentate gyrus granular cell layer was of a similar thickness and pattern of asymmetry as the males. Male rats also had a higher density of apical excrescences and greater branching of dendrites of CA3 pyramidal hippocampal neurons than did female rats (Gould, Westlind-Danielsson, Frankfurt & McEwen, 1990).

Other sex differences in the structure of the hippocampus in rats are dependant on the environment in which the animal is reared. For example, females reared in a complex environment had significantly more branching in the middle region of the dendritic tree in the dentate gyrus than those reared in an isolated condition, whereas in males there were few differences in dendritic branching between the two environments (Juraska, 1991). This may suggest that the female hippocampus shows significantly more plasticity than does the male hippocampus. When male rats were castrated at birth, they showed patterns of dendritic branching similar to the normal females, in that they evidenced greater plasticity to the environment in which they were raised (Juraska, 1991). It would seem from these studies that T, acting either

during development or around puberty, suppressed much of the response of the dendritic tree to the enriched environment.

The size of the corpus callosum in rats is also influenced by neonatal T levels, since injections of T to rats neonatally increased the size of the corpus callosum attained in adulthood (Fitch, Cowell, Schrott & Denenberg, 1991). In humans, a positive correlation was found between free T levels and the size of the corpus callosum as assessed by MRI in young adult males, which the authors attributed to early organizational effects of T exposure (Moffat, Hampson, Wickett, Vernon & Lee, 1996). The splenium, the most posterior portion of the corpus callosum, was initially reported as larger and more bulbous in women than in men (deLacoste-Utamising & Holloway, 1982). However, this distinction has been called into question as several studies found that males had a larger splenium (Witelson, 1991). The isthmal region of the corpus callosum, where interhemispheric axons pass between right and left posterior parietal and superior temporal regions, does, however, appear to be larger in women than in men, particularly in right-handers (Witelson, 1991).

As early as 13 weeks into gestation, the entire right cortex in male fetal brains and the prefrontal cortex in female brains were more developed relative to other brain regions (deLacoste & Horvath, 1985). Other sex differences found in humans include the finding that men had a larger weight difference between the left and right brain hemispheres than did women (Hampson & Kimura, 1992), that the nuclei of the preoptic anterior hypothalamic area was larger in males than in females (Allen, Hines, Scryne & Gorski, 1989), and that the anterior commissure was larger in females than

in males (Allen & Gorski, 1986). However, these effects of early exposure to T are often acting via its conversion to E_2 in the brain, as described in the section on the metabolism of T.

A sex difference in GRs in the hippocampus has also been found, in that female rats have a greater number of GRs in this area (Turner & Weaver, 1985). Additionally, OVX resulted in an increased concentration of hippocampal GR receptors, while castration in the male had no effect on GR binding. This indicates that female rats may be more susceptible to the damaging neuronal effects of CRT administration than males, and that this sex difference may be exacerbated by OVX. Indeed, adrenalectomy following hippocampal lesions resulted in an increased sprouting response in the hippocampus of female rats, but had no effect on male rats, indicating that adrenal hormones inhibited neuronal plasticity in the female hippocampus (Scheff, Morse & DeKosky, 1988b).

Behavioural Studies of Steroid Action

Estrogen and Memory

Animal studies:

Organizational Effects - Sex differences

There are a great many animal studies investigating the effects of estrogen administration on cognition in a variety of non-human species, including birds, rodents and non-human primates. These studies can be divided into those that investigated early organizational effects of E_2 and those that examined later activational effects. In a typical study investigating organizational effects of hormones in rodents, animals

are castrated or OVX at birth when the brain is still developing, and subsequent behaviour of these animals is compared to normal controls. Often steroids will be administered later to mimic the normal hormonal milieu in an attempt to isolate the early effects of steroid deprivation. Alternatively, animals are treated *in utero* with different hormone preparations given to the mother and the later behavioural consequences observed. These methodologies alter the hormonal environment of the animal during an early stage of brain development in order to affect the "hard-wiring" of the brain.

In contrast, studies of the activational effects of hormones usually investigate the effects of steroid administration in adult animals. Animals may be castrated in adulthood, and given replacement doses of various hormonal treatments. In this way, comparisons between animals suddenly deprived of hormones and those remaining intact can be made, and by later reinstating normal hormone levels investigators can determine whether these effects are reversible. These studies investigate the relationships between levels of specific hormones and relatively temporary fluctuations in behaviour compared to the more permanent alterations in brain morphology investigated in organizational studies. Because the studies reported in this dissertation investigated activational effects of steroids on memory, other activational studies will be the focus of this review.

First, however, the findings of the organizational effects of estrogens on animals will be briefly reviewed. As reported previously, several sex differences in brain morphology between males and females exist. So, too, are there sex differences

in various cognitive functions. On learning and memory tasks that require the use of spatial cues, male rats consistently perform better than females, acquiring the task more rapidly and generally exhibiting superior performance (Aggleton, Blindt & Candy, 1989; Williams, Barnett & Meck, 1990; vanHaaren, vanHest & Heinsbroek, 1990; Luine & Rodriguez, 1994). Even following gonadectomy in adulthood, male rats still outperformed female rats on radial arm maze learning (Luine & Rodriguez, 1994; Williams et al, 1990). This is thought to be due to the perinatal exposure of male rats to high levels of E_2 through the aromatization of testicular T (Williams et al, 1990; Roof & Havens, 1992; Luine & Rodriguez, 1994; McEwen et al, 1996).

Female rats are more active than males on the running wheel and in the open field, while male rats show more active play behaviour than females (van Haaren at al, 1990). Female rats are also better at active avoidance learning than male rats (e.g. Beatty & Beatty, 1970), and learn to perform a low rate responding task more efficiently than do males (van Hest, van Harren & van de Poll, 1987). The latter two gender differences favoring females may be due, at least in part, to the sex difference in general activity. However, there is some evidence to suggest that the female advantage in active avoidance learning may be due to a negative influence of androgens prenatally because castration of the male rate improves performance, while treatment of the female rat with T impairs performance on this task (Beatty, 1979).

Activational Effects:

Several recent studies have focussed on the activational effects of estrogens on learning and memory in rodents. Gonadally intact adult male rats injected with E_2

valerate showed enhanced short-term (10 minute) and long-term (24 hour) memory of one-trial passive-avoidance conditioning compared to untreated rats (Vazquez-Pereyra, Rivas-Arancibia, Castillo & Schneider-Rivas, 1995). Similarly, a post-training intrahippocampal injection of E_2 to male rats resulted in lower latencies to escape in the Morris water maze 24 hours later (Packard, Lohlmaier & Alexander, 1996). When the cholinergic antagonist scopolamine was injected after E_2, the enhancing effects were blocked, suggesting that E_2 was enhancing memory via the cholinergic system in these male rats (Packard et al, 1996). Post-training scopolamine treatment caused adult OVX rats to perform poorly in a previously learned T maze, but pretreatment with E_2 reversed the deficits induced by scopolamine (Dohanich et al., 1994). After 5 and 28 weeks of estrogen treatment, OVX rats performed more accurately and learned faster in an active avoidance paradigm than control rats and OVX rats who did not receive estrogen (Singh et al, 1994). However, Morris water maze performance was not different between the groups, suggesting that while in males the cholinergic system may mitigate maze learning (Packard et al, 1996), in females it may mediate active avoidance behaviour.

In an attempt to resolve some of the inconsistencies found between male and female rats, Luine & Rodriguez (1994) administered E_2 or placebo to aged gonadally intact male and female rats and also to gonadectomized young males and females, then tested their radial arm maze learning speed and accuracy. E_2 enhanced performance in both young and aged male rats in trials that required a delay component, but did not enhance performance in the female rats. In summary, these findings suggest that E_2

enhances spatial memory in male rats (Vazquez-Pereyra et al., 1995; Packard et al, 1996; Luine & Rodriguez, 1994) and performance in non-spatial learning tasks in female rats (Singh et al, 1994) although not all results are consistent with this conclusion (e.g. Dohanich et al., 1994).

Human studies

Sex differences in cognition:

Gender differences in cognitive performance are seen from a very early age in humans, although in some cases they become stronger around the time of puberty. In general, men tend to perform slightly better than women on tasks of spatial and quantitative abilities, while women show better fine motor control, perceptual speed, and excel at some verbal skills (Jarvick, 1975). In a meta-analysis, Linn & Peterson (1985) concluded that the largest sex differences favoring males occurred in tests of mental rotations. The overall magnitude of this sex difference was one standard deviation, which is considered to be a large effect (Cohen, 1977). Tests of spatial perception showed a sex difference ranging in size from one third to two thirds of a standard deviation unit, a medium size effect. Very small sex differences favoring males occurred in tests of spatial visualization. All of these differences existed before puberty and lasted into adulthood, becoming larger after the age of 18 in some instances.

Hyde and Linn (1988) analyzed the results of 165 studies of sex differences in various types of verbal ability. There was an overall effect size in favor of females of +0.11 SD, which they characterize as very small though significant. Indeed,

compared with the effect sizes found in other studies investigating gender differences in spatial ability, aggressiveness and helping behaviour, this effect is one of the smallest sex differences in the literature.

Sex differences have also been found in functional brain organization, such that certain cognitive functions appear to be supported by slightly different brain areas in men and women. These differences occur both interhemispherically, between the left and right hemispheres, and intrahemispherically, between the anterior and posterior regions within the left hemisphere. In most right-handed humans, the left side of the brain is considered to be primarily responsible for the control of speech and some manual movements, while the right hemisphere is differentially responsible for other non-verbal functions (Hampson & Kimura, 1992). Women tend to show a more bilateral representation of cognitive functions than men, whereas men show a greater degree of cerebral lateralization than women (McGlone, 1980). This is consistent with the finding that women have a larger corpus callosum, the connective pathway between the two hemispheres, than do men (deLacoste-Utamising & Holloway, 1982).

Consistent with these findings, damage to the left hemisphere resulted in more impairment of verbal IQ in men than in women, whereas damage to the right hemisphere impaired verbal IQ in women but not men (McGlone, 1978). Moreover, only males showed deficits on a test of verbal proverbs following lesions to the left temporal lobe (Lansdell, 1961). Experiments using dichotic listening and tachistoscopic techniques have also concluded that women have smaller auditory and visual perceptual asymmetries than men (McGlone, 1980).

There are some studies which show sex differences in intrahemispheric organization of cognitive functions. Within the left hemisphere, the anterior region may be more important for the production and decoding of speech in females than the posterior region. Kimura (1983) found that aphasia and manual apraxia in women resulted more often from damage to the anterior rather than the posterior part of the left hemisphere. However, in men there was no distinction between the cognitive deficits incurred from anterior versus posterior left hemispheric lesions. Although it appears that cognitive functions are supported by slightly different brain structures in men versus women, many questions remain. Are these functional differences due to the early organizational effects of steroid hormones? If so, are they related to the structural differences found between male and female brains? Are these gender differences in cerebral structure and function responsible for the sex differences in cognitive abilities? Some of the studies on organizational effects of gonadal hormones allow partial answers to these questions, but they are by no means resolved.

Organizational Effects:

Clearly, it is difficult to investigate organizational effects of hormones in humans due to the obvious ethical problem of altering the prenatal hormonal milieu. To circumvent this problem, researchers often investigate populations exposed to abnormal prenatal hormonal environments, such as females with congenital adrenal hyperplasia (CAH), who suffer an adrenal 21-hydroxylase deficiency which results in exposure to high levels of androgens prenatally. CAH women tend to show an advantage in visual and spatial tasks such as mental rotations, card rotations and

embedded figures compared to age and IQ matched controls (Nass & Baker, 1991; Resnick, Barenbaum, Gottesman & Bouchard, 1986). On the other hand, hypogonadal men who were exposed to only low levels of T in utero have reduced visuospatial abilities compared to matched controls and to men who became hypogonadal postpubertally (Hier & Crowley, 1982). These results indicate that early T exposure "masculinizes" cognition later in life in women, and lack of T in utero "feminizes" cognition in men.

Other populations that have been studied include women and men exposed *in utero* to diethylstilbestrol (DES), a synthetic estrogen. In women, DES exposure later in fetal life was more likely to lead to a pattern of cognitive masculinization than early fetal exposure (Hines & Sandberg, 1996), and any DES exposure masculinized performance on a dichotic listening task (Reinsch, Zeimba-Davis & Sanders, 1991). Men exposed to DES had worse spatial ability and less hemispheric laterality compared to controls, indicative of cognitive feminization (Reinsch et al., 1991).

Activational effects: menstrual cycle studies

The menstrual cycle provides an opportunity to examine naturalistic fluctuations of hormone levels in women. The first day of menstruation is termed day one of the menstrual cycle. The follicular phase (Days 1-14) has been divided into two stages, the menstrual stage and the pre-ovulatory stage, which occurs on days 12-14 just prior to ovulation. E_2 and P are at their lowest levels during the menstrual stage and increase gradually throughout the follicular phase. E_2 rises to a high peak just prior to ovulation and then falls. During the approximately 14-day luteal phase (Days 15-

28), E_2 and P increase gradually and then decrease just prior to the onset of menstruation on day 28. Thus, there are several distinct hormonal phases throughout the cycle that provide opportunities to compare cognitive functioning.

A number of methodological issues are inherent in the available menstrual cycle studies which have led to inconsistencies in the literature. Problems commonly found in the research include 1) failure to directly measure hormone levels by radioimmunoassay, relying on self-report or indirect measures to ascertain menstrual cycle phase, 2) use of cognitive tests that are inappropriate for detecting the expected changes in performance, 3) small sample sizes, 4) use of idiosyncratic terminology for identifying days of the cycle, 5) testing women at times in the cycle that are inappropriate to investigate the hypothesis of interest, and 6) failure to consider concurrent menstrual symptoms that may interfere with test performance, such as premenstrual dysphoria or menstrual cramps.

The strongest evidence for differences in cognitive performance between cycle phases is found on spatial tasks which generally show a more consistent sex difference favoring men (Linn & Peterson, 1985). Women performed worse during the pre-ovulatory estrogen surge than during the menstrual phase on the Embedded Figures test (Komnenich, Lane, Dickey and Stone, 1978; Broverman et al., 1981), and on a composite score of spatial orientation, spatial visualization and flexibility of closure (Hampson & Kimura, 1988; Hampson, 1990a; Hampson, 1990b), suggesting that the high E_2 levels of the pre-ovulatory surge may have caused the decrement. However, Gordon & Lee (1993) failed to find any differences in performance on tests measuring

geometric rotations in space, imagining blocks in three dimensional space or perceptual closure between the menstrual, ovulatory and luteal phases of the cycle.

During the menstrual phase, women scored worse on the delayed visual reproduction test, which measures visual memory, compared to during the late luteal phase (Phillips and Sherwin, 1992a). This change was positively correlated with plasma P levels in the luteal phase, and showed no correlation with E_2 levels. This suggests that P may be beneficial to spatial memory performance in regularly cycling women.

Enhanced performance of simple verbal-articulatory skills have been reported during periods of higher E_2 (Hampson, 1990a, 1990b; Anderson, 1972; Snyder, 1978; Broverman et al., 1981), but more complicated verbal skills such as vocabulary or grammar did not vary across the cycle (Hampson & Kimura, 1992). No differences in verbal *memory* performance were found across cycle phases in most studies (Phillips & Sherwin, 1992a; Hartley, Lyons & Dunne, 1987; Keenan, Lindamer & Jong, 1995; Keenan, Stern, Janowsky, & Pedersen, 1992; Morgan, Rapkin, D'Elia, Reading, & Goldman, 1996), although a positive correlation between E_2 levels and Paired-Associate scores occurred in one study (Phillips & Sherwin, 1992a). Taking into account the discrepant findings, it appears that the fluctuations in hormone levels across the menstrual cycle do not consistently affect verbal memory performance in normal healthy women.

To summarize, there is evidence to suggest that the fluctuations of E_2 and P that occur over the 28 days of the menstrual cycle can affect performance on some

cognitive tasks. Spatial skills, on the whole, appear to be better during the menstrual phase of the cycle, when E_2 and P are low, and worse during the pre-ovulatory and luteal phases, both of which are characterized by higher E_2, thus suggesting a causal role for E_2. Although P may also be involved in spatial functions, the particular relationship remains to be clarified. Simple verbal articulatory and perceptual abilities may be enhanced during periods of the cycle characterized by higher E_2. However, neither verbal nor spatial memory are consistently affected by the phase of the menstrual cycle.

Transsexual hormone treatment

In a study of transsexuals undergoing hormone treatment, Van Goozen, Cohen-Kettins, Gooren, Frijda, & VandePoll (1995) studied 35 female to male (FM) and 15 male to female (MF) transsexuals before and after a three month course of treatment. Ss were compared to groups of age matched heterosexual men and women. Those in the FM group received T injections once every two weeks, and those in the MF group were given both anti-androgens and estrogens orally twice daily.

Biological females performed better than males on verbal fluency tests, but there were no sex differences in visuospatial ability. Verbal fluency scores decreased and rotated figures performance increased in the FM group after three months of treatment, while the verbal fluency scores remained stable and rotated figures scores decreased slightly in the MF group. Unfortunately, the authors did not test either verbal or visuospatial memory performance in these subjects. However, this study provides compelling evidence that T improves visual-spatial functioning and E_2

(coupled with low T) improves verbal fluency.

Recall that prenatal exposure of the brain to E_2 and T both lead to masculinization of cognitive functions. In adulthood, however, these results demonstrated that T masculinizes cognitive functions in both men and women, while E_2 feminizes functions. Whether this generalization applies to aspects of memory as well as to general verbal and visuospatial skills is unknown at the present time.

"Add-Back" Estrogen Treatment

Women with uterine myomas are often treated with a gonadotropin releasing hormone (GnRH) analog, which causes tumors to shrink by suppressing ovarian secretion of E_2. In this manner, the shrunken myoma can be removed without resorting to invasive surgery. However, the complete suppression of the ovary leads to uncomfortable symptoms related to hypoestrogenism, which can be relieved by small "add-back" doses of estrogen while still suppressing the ovarian secretion of gonadal steroids. Women who were to undergo this surgery were treated for 12 weeks with the GnRH analog LAD, after which they were randomly assigned to either LAD plus estrogen or LAD plus placebo for an additional 8 weeks, and their cognitive functioning was tested at baseline, after 12 weeks of LAD and after 8 weeks of combined treatment (Sherwin & Tulandi, 1996)

Scores on Immediate and Delayed Paragraph Recall and Immediate Paired Associates decreased after 12 weeks of ovarian suppression in these women, concomitant with decreasing levels of E_2. After the add-back phase, the scores of the group who received E_2 in addition to LAD returned to baseline levels, whereas scores

for the LAD plus placebo group remained depressed in concordance with their low E_2 levels. None of the other tests scores in the comprehensive test battery changed over the course of the study. These results strongly suggest that E_2 enhances explicit verbal memory functions in women.

Postmenopausal studies

The menopause provides an opportunity to study the possible effects on cognition of a drastically changing hormonal milieu. At the time of the menopause (average age 51 years), women's estrogen levels decrease dramatically (Longcope, 1986). Because of research demonstrating the clinically beneficial effects of estrogen replacement therapy (ERT) for maintaining bone density, protecting against heart disease and eliminating many distressing and uncomfortable symptoms of menopause, the practice of prescribing ERT has become increasingly common. This provides a unique paradigm to investigate the cognitive effects of estrogen in this population.

Some studies have used tasks that measure explicit memory in postmenopausal women. Healthy 64 year-old postmenopausal estrogen-users performed better on both Immediate and Delayed Paragraph Recall tests than non-users matched for age and education (Kampen & Sherwin, 1994), but there was no effect of estrogen therapy on any of the visual memory tests administered in that study. Estrogen administration to nine menopausal women improved performance on the Guild Memory Scale, which measures immediate and delayed verbal memory, compared to nine controls who were administered placebo (Hackman & Galbraith, 1976). In a controlled study, Campbell & Whitehead (1977) administered E_2 daily for two months to postmenopausal women

and found that estrogen improved memory more than placebo. However, the measure of memory functioning was a self-report analogue scale, which does not allow for firm conclusions regarding the role of estrogen on memory.

On a test of proper name recall, where participants were exposed to slides of faces and attempted to remember the person's name, the performance of 67 year-old female estrogen-users was better than that of non-users matched for age and education (Robinson, Friedman, Marcus, Tinklenburg & Yesavage, 1994). This latter study is the only one that has shown explicit memory effects in areas other than verbal memory, although there are both verbal and non-verbal components to the face-naming task. Thus, it appears that the majority of the enhancing effects of E_2 on explicit memory seem to be specific to verbal memory.

In terms of non-declarative memory, an epidemiological study of 800 elderly women found that those who had been using estrogen for at least twenty years performed significantly better on the test of Category Retrieval, which measures language fluency and semantic memory, compared to those who had never used estrogen (Barrett-Connor & Krtiz-Silverstein, 1993). Other clinical trials have also reported an estrogenic enhancement of other, non-memory cognitive skills in elderly women (Caldwell & Watson, 1952; Kantor, Milton & Ernst, 1973; Campbell & Whitehead, 1977; Fedor-Freybergh, 1977). A variety of cognitive measures showed improvement in these studies, including the verbal, but not visual, subtests of the Wechsler-Bellevue intelligence test (Caldwell & Watson, 1952), standardized reaction time and attention tests (Fedor-Freybergh, 1977), and other more subjective measures

such as communication skills, self care, work and daily activities (Kantor et al., 1973). Most of these studies had small sample sizes and some were uncontrolled. In the Caldwell & Watson (1952) study, one year after estrogen was withdrawn, scores of all the women decreased relative to their baseline scores two years earlier, indicating that the beneficial effects of ERT were evident only as long as the hormone was being administered.

Other researchers have reported contradictory findings. No differences occurred between estrogen-treated and placebo-treated women on the Raven's Progressive Matrices, a test of general IQ (Raumaro, Lagerspetz, Engblom, & Punnonen, 1975), on the Benton Visual Retention Test, the Digit Span Test, the Digit Symbol Test, or on concentration tests (Vanhulle & Demol, 1976; Ditkoff, Crary, Cristo & Lobo, 1991). However, methodological inconsistencies in these clinical studies make interpretation of their findings difficult. Nonetheless, if E_2 were acting on medial temporal lobe memory systems, effects on general IQ or on general visuospatial skills would not be expected, nor would enhancement of Digit Span, as performance on this test is not significantly impaired after hippocampal lesions (Moscovitch, 1982). Nonetheless, it is unclear if, in the Ditkoff et al. (1991) study, the authors assessed both Forward and Backward Digit Span or whether the results differed on these sub-tasks. Forward Digit Span is considered to be a test of short-term memory, attention and concentration while backward Digit Span requires working memory skills as well as short-term memory. Therefore Forward and Backward Digit Span are likely quite different and thus these subtests should be assessed independently.

It is difficult to formulate a general conclusion regarding this literature because there are many methodological issues to be considered, as outlined by Sherwin (1996). Briefly, these include differing routes of estrogen administration, differing trial lengths, different estrogen preparations and doses, different age groups of women tested, failure to directly measure hormone levels, and different psychometric instruments used to measure vastly differing cognitive abilities.

More recent and better controlled studies have used populations of premenopausal women about to undergo total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO) for benign disease. One such study included standardized cognitive assessment and measurement of plasma hormone levels at baseline prior to the operation, when the hormone levels were within the range of normal cycling women, followed by random assignment to a placebo or treatment group (10 mg estradiol valerate intramuscularly) postoperatively. Treatment continued for three months followed by a one month placebo washout period, then a crossover occurred in which each woman received the other treatment (placebo or ERT) for a further three months. Levels of plasma estradiol were monitored throughout the protocol, and standardized cognitive testing was performed after the first three months and again after the final three month trial (Sherwin, 1988a). Scores on Paragraph Recall were maintained in the ERT women pre- to post-operatively, while those receiving placebo showed significant decreases in Paragraph Recall, concomitant with the dramatic decreases in estrogen precipitated by the surgery (Sherwin 1988a).

In a similar study, Sherwin & Phillips (1990) found that Paired-Associate

scores were maintained in ERT women two months postoperatively, but were significantly decreased in the placebo group. Further, scores on Paragraph Recall increased in the ERT group while the placebo group maintained preoperative performance levels. There were no differences pre- to post-operatively on measures of visual memory. Finally, Phillips & Sherwin (1992b) reported another study with a larger group of women which found that, by the third postoperative month, scores on both Immediate and Delayed Paired-Associate learning had decreased significantly in the placebo group, but were significantly better in the estrogen treated group. These studies support the assertion that estrogen treatment in surgically menopausal women helps to maintain and perhaps even facilitate specific aspects of explicit verbal memory.

To summarize the studies of postmenopausal women to date, there is considerable evidence from well-controlled studies that ERT is associated with better performance on some tests of explicit memory, primarily on tasks such as Paragraph Recall that assess verbal memory and on non-declarative memory tasks such as Category Retrieval that assess verbal semantic memory.

There have been no studies investigating the role of E_2 in elderly men, although men likely have higher E_2 levels after the age of 50 than do women. For this reason, the studies in this dissertation are the first that have specifically included groups of elderly men as well as women estrogen-users and non-users to investigate the relationships between E_2 and cognition.

Testosterone and Memory

Animal studies:

In the developing male brain, T appears to organize spatial memory functioning through its aromatization to E_2 by influencing the development of the hippocampus (Roof & Havens, 1992; Williams & Meck, 1993). On the Morris water maze, males outperformed females at age 90+ days. However, when T was administered on postnatal days 3 and 5, treated females performed better than control females and both treated and untreated males at 90+ days, whereas treated males had small decrements compared to control males (Roof & Havens, 1992).

How fluctuations in T levels in adulthood affect performance is unclear in humans, although the picture is more definitive in other animal species. T improved spatial memory in adult male rodents (Flood, Morley, & Roberts, 1992), and improved both learning and retention of a footshock avoidance task in elderly mice who otherwise showed significant age-dependant impairment on the task (Flood, Farr, Kaiser, Regina & Morley, 1995). When given to young domestic male and female chicks, T improved performance in a passive-avoidance task designed to measure memory and attentional processing (Clifton, Andrew & Raney, 1986), and facilitated long-term memory retention in a similar passive-avoidance discrimination task (Gibbs, Ng, & Andrew, 1986). Therefore, in rodents and chicks T appears to facilitate a variety of learning and memory behaviour in both males and females.

Human studies:

While it is the case that men of all ages generally outperform women on spatial tasks (Jarvik, 1975), it is not necessarily the case that T fluctuations in adult life have

activating effects on these same skills, either in men or women, although some authors have suggested this possibility (Hampson & Kimura, 1992). It has been suggested alternatively that T levels are linearly related to performance (Christiansen & Knussman, 1987), curvilinearly related to performance (Gouchie & Kimura, 1991), or effective only above a certain threshold level (Bancroft, 1988).

Circulating T levels were positively associated with visuospatial orientation (Gordon & Lee, 1986) and composite visuospatial scores (Errico, Parsons, Kling & Kling, 1992) in men. Administration of T to elderly men for three months enhanced their spatial cognition compared to a matched group given a placebo (Janowsky, Oviatt, & Orwoll, 1994). However, other investigators failed to find significant correlations between T and aspects of cognitive performance, including spatial and visual skills (Kampen & Sherwin, 1996; McKeever, Rich, Deyo, & Connor, 1987; Gordon, Corbin, & Lee, 1986). A recent study reported by Alexander (1996) investigated cognitive abilities in hypogonadal and eugonadal men prior to and following exogenous T administration in a manner that allowed testing of the three aforementioned theories of T action. The results did not support the hypothesis that androgens activate cognitive functioning, since performance did not improve in any of the groups after T administration. However, the hypogonadal men performed worse on tests of visuospatial ability than the eugonadal men, supporting the hypothesis that early hormone exposure plays a role in the development of sex-typed behaviors.

In summary, the findings regarding the role of T in cognitive performance and memory provide strong support for the notion that T acts upon the developing brain

to stimulate sex-typed behaviour later in life, but are inconsistent with respect to possible activational effects of T. Few studies have specifically investigated the relationship between components of *memory* and T levels in either men or women.

Cortisol and memory:

Animal Studies:

Many studies have investigated the detrimental effects of CRT on the hippocampus in rodents and primates, but relatively few have investigated behaviour as well. Corticosteroid administration impaired performance on maze learning (Landfield, Baskin & Pitler, 1981) and forced extinction (Borrell, deKloet & Bohus, 1984) in rats. Adrenalectomized (ADX) rats have learning and memory deficits that can usually be ameliorated by administering epinephrine. However, when corticosterone was administered to ADX rats prior to learning a passive avoidance task, epinephrine failed to improve the impairment (Borrell et al., 1984). As well, pretreatment with corticosteroids blocked the memory-improving effects of nootropics and cholinomimetics in a paradigm of step-down passive avoidance in mice (Mondadori, Ducret & Hausler, 1992). These classes of drugs have been used in animal studies and with AD patients to improve memory, but their usefulness in AD is controversial (Mondadori et al, 1992).

Human Studies:

The human research investigating the cognitive effects of CRT is compelling. Individuals with Cushing's Syndrome have a chronic elevation of corticosteroids and therefore provide a useful model for studying the cognitive effects of

hypercortisolemia. Twelve people with Cushing's syndrome showed cognitive impairments on tests of verbal and visual immediate and delayed recall from the WMS (Starkman et al., 1992). Moreover, the magnitude of these impairments was positively correlated with hippocampal formation volume as measured by MRI (Starkman et al., 1992). This confirmed an earlier report of memory impairments in Cushing's Syndrome patients (Whelan, Schteingart, Starkman & Smith, 1980). Another study of 25 Cushing's Syndrome patients found impaired performance on tests of Immediate and Delayed Paragraph Recall, Backward Digit Span, Visual Reproduction and the Digit Symbol Substitution Test compared to normal controls (Mauri et al., 1993). Following six months of treatment which reduced CRT levels to normal in eight patients, a significant improvement in Immediate and Delayed Paragraph recall, Forward Digit Span and the Digit Symbol Substitution Test was found.

Some studies have directly investigated the effects of treatment with exogenous CRT to a variety of populations. Twenty-seven asthmatic children each received a high and a low dose of prednisone (61.5 mg/day and 3.33 mg/day, respectively), a synthetic corticosteroid. The only memory test used was the Selective Reminding Test, which assesses immediate and delayed verbal memory. Only the high dose of corticosteroid was associated with decreased verbal memory and increased depression and anxiety (Bender, Lerner, & Kollasch, 1988). When 1 mg DEX (synthetic cortisol) was given to 49 healthy volunteers, a significantly higher rate of errors of commission and intrusions into free recall on a list learning task occurred in the DEX treated group compared to those who received placebo (Wolkowitz et al., 1990). Similarly, when

11 volunteers received prednisone (80 mg/day) for five days, the same increase in commission errors occurred. However, scores returned to normal 7 days after discontinuation of the treatment (Wolkowitz et al, 1990). Four days of treatment with DEX (0.5, 1, 1, 1 mg) resulted in a decrease in scores of both Immediate and Delayed Paragraph Recall compared to placebo, followed by posttreatment recovery to baseline scores (Newcomer, Craft, Hershey, Askins, & Bargdett, 1994), suggesting a selective effect of DEX treatment on verbal declarative memory function.

Higher CRT levels and compromised cognitive performance, including memory, also occur frequently in individuals with major depressive disorder (Sikes et al., 1989). After an injection of 1 mg DEX, depressed subjects who were non-suppressors of cortisol, indicating a dysfunction in the feedback of the HPA axis, showed a higher rate of errors of commission on the verbal memory task than did depressed suppressors and control subjects (Wolkowitz et al., 1990).

In a naturalistic study of 19 healthy elderly people (11 men and eight women), subjects who showed a significant increase in CRT levels over five years and whose CRT levels were high at the time of testing were impaired on Paired Associates and selective attention tasks compared to those with stable or decreasing levels of CRT across time (Lupien et al., 1994). None of the other tasks that were assessed, including WMS Paragraph Recall, Visual Reproduction, Digit Span, Verbal Fluency, Picture Naming or Implicit memory showed any differences between groups. Only the combination of an increasing slope of CRT levels coupled with high concurrent CRT was predictive of impaired performance in this study.

Finally, O'Brien, Schweitzer, Ames, Tuckwell & Mastwyk (1994) administered 1 mg DEX to 33 older subjects aged 51-96 years. They assessed cognitive function prior to the DEX test using the Cambridge examination for mental disorders in the elderly, which contains a cognitive examination that measures language and memory, as well as orientation and praxis. The day following DEX administration, they measured CRT and DEX levels but did not re-evaluate cognitive functions. Age was positively correlated with post-DEX CRT, indicating a dysregulation of HPA feedback with advancing age. Both age and CRT levels were negatively correlated with cognitive scores.

Taken together, these studies provide evidence that exposure to high CRT levels may result in cognitive impairments, particularly in explicit memory functions reliant on the hippocampus, in both healthy and clinical populations, and that there may be some dysregulation in HPA feedback with advancing age. These findings support Sapolsky et al.'s (1986) glucocorticoid cascade hypothesis of memory dysfunction.

One study, however, found both beneficial and detrimental effects of CRT administration on memory. Administration of different doses of hydrocortisone to eighty male undergraduates sixty minutes prior to list learning resulted in facilitation of early word list recall at all doses (5, 10, 20 and 40 mg; Beckwith, Petros, Scaglione & Nelson, 1986). The design of this study included the successive presentation of ten different word lists, with recall tested immediately after the presentation of each list. For the first half of each list, recall was facilitated by all dosages, but for the last half of the lists, those who received 40 mg doses did better, while those receiving 5 mg did

worse. These results are inconsistent with those of other studies of steroid administration that found detrimental effects on memory of high doses of prednisone (80 mg/day, Wolkowitz et al, 1990; 61.5 mg/day, Bender et al., 1988). The authors attributed their results to possible activating/arousing effects of CRT.

DHEAS and memory:

Animal Studies:

Because of the effects of DHEAS on the GABAergic system, it was thought that DHEA/S administration might influence cognition. When mice were given DHEAS or placebo three minutes after training in an active avoidance T-maze paradigm, then retested one week later, those who received DHEAS showed better retention of the training (Roberts et al., 1987). Similarly, Flood et al., (1992) found that post-training administration of DHEA/S to male mice resulted in improved retention of footshock active avoidance training.

When 55 day old OVX rats were injected with DHEAS, those given 6.4 mg/kg of DHEAS performed better than vehicle injected animals on a delayed non-matching to sample task, but not on the Morris water maze (Frye & Sturgis, 1995). Therefore, DHEAS enhanced working/ long-term memory, but not spatial/ reference memory, which is consistent with results of other studies in this area suggesting that DHEAS administration to rats enhances long-term memory.

Human Studies:

Cognitive effects of DHEAS have been investigated in several studies of human populations. When given in replacement doses to elderly men and women, 50 mg/day

DHEAS improved subjective measures of psychological well-being as well as immune function (Morales, Nolan, Jerald, Nelson, & Yen, 1994; Yen, Morales, & Khorram, 1995). However, objective memory functions and mood were not assessed. DHEAS levels of male nursing home residents were inversely related to the presence of organic brain syndrome (AD, multi-infarct dementia and other types) and to the degree of dependance in activities of daily living (Rudman, Shetty & Mattson, 1990).

In a community sample of elderly men and women, Barrett-Connor and Edelstein (1994) measured DHEAS from blood samples taken from 270 men and 167 women between 1972 and 1974. Subjects were tested 16 years later on the Buschke Selective Reminding test, visual reproduction, trailmaking, Category Fluency and the Mini Mental Status Examination. A positive correlation occurred between DHEAS levels and performance on the delayed Selective Reminding Test in the women only, which was dismissed as a spurious result. The failure of these authors to re-assess DHEAS levels at the time of retesting after the 16 year delay renders these results uninterpretable, especially since DHEAS production decreases with increasing age (Hornsby, 1995; Vermeulen, 1995).

After four weeks of an open trial of DHEAS administration to six clinically depressed men and women, the patients were significantly less depressed, and their scores on a measure of automatic memory processing had improved, but scores on tasks of explicit verbal memory performance did not change. Because there was no control group, the possibility that any changes in memory may have occurred secondary to the alleviation of depression cannot be ruled out. Other investigators

found preventative effects of DHEAS on physical outcomes such as mortality (Barrett-Connor, Khaw, & Yen, 1986), coronary heart disease (Lacroix, Yanno & Reed, 1992) and immune function (Casson et al., 1993), but did not investigate cognition.

Several studies have investigated DHEAS, CRT and memory in AD patients, which will be discussed in the section on AD.

Aging and Memory

Aging in the Brain:

The process of normal aging in humans is accompanied by many changes in the structure as well as the biochemistry of the brain. Structural changes include weight loss, atrophy and increased ventricular volume (Winblad, Hardy, Backman & Nilsson, 1985). The average reported weight loss in the brains of elderly subjects is 7-8% of peak adult weight (Creasey & Rapoport, 1985). PET and MRI technologies have made it possible to assess changes in the aging brain *in vivo*. Age-associated decrements in brain matter volumes of healthy subjects were found in the cerebellum, cerebral hemispheres, parieto-occipital lobe, parahippocampal gyrus, amygdala, thalamic nuclei and caudate nuclei using MRI, as well as bilateral increases in volume of ventricular and peripheral cerebrospinal fluid (Murphy et al., 1996). Age-associated decrements in glucose metabolism of whole-brain, frontal, temporal and parietal regions were asymmetric in parietal (left more affected than right) and frontal (right worse than left) lobes, as well as in language areas (Broca's area more affected than Wernicke's area).

Others who studied sex differences in the aging brain with MRI reported that

men had a significantly greater age-related volume loss in the whole brain and in the frontal and temporal lobes, whereas loss was greater in women in the hippocampus and parietal lobes (Murphy et al., 1996). In a PET study, women showed a greater age-related metabolic decline in the thalamus and hippocampus than men. Generally, men evidenced greater age-related metabolic declines in the left hemisphere, while in women the aging effect was either equal in the two hemispheres or greater in the right (Murphy et al., 1996). If women experience more damage to hippocampal structures with aging, and the integrity of this structure is necessary for declarative memory functions, it might be expected that women would show a greater memory loss than men with advancing age, and that men would experience a more general detriment in language abilities and/or frontal functions. Indeed, a higher incidence of AD has been reported in women (Jorm, Korten, & Henderson, 1987) and nondemented elderly men show a greater deterioration of verbal functions than do women (West et al., 1992).

Alzheimer's Disease

AD is the most prevalent form of dementia, with reported prevalence rates ranging from 0.2% to 3.0% of the population under age 75 and from 7.1% to 47.3% over age 85 (Keefover, 1996), and is more prevalent in women than men (Jorm et al., 1987). The age-specific incidence rates of AD in women vary from 1.5 to 3.5 times that of men across multiple studies and ethnic groups (Birge, 1996). Increasing age is a risk factor for this disease, and the higher prevalence of women is most apparent after the age of 65. Most studies that failed to find a sex difference in the incidence of AD have been conducted on younger samples, which are likely to contain more

instances of familial AD, which may be less related to hormonal status (Birge, 1996).

Neurological Effects:

AD is characterized by many gross changes in the brain, of which the most common is cortical atrophy, which involves shrinkage of the gyri and widening of the sulci, primarily within the frontal and temporal lobes, but sometimes extending to parietal and occipital regions (Mann, 1988). This shrinkage is thought to be due to cell death in these areas (VonDrass & Blumenthal, 1992). Substantial cell loss has been reported in the frontal, cingulate and temporal gyrus, and the hippocampus and amygdala (Mann, 1988). In the hippocampus, there is approximately 40-47% reduction in total cell numbers (Ball, 1976; Mann, Yates & Marcyniuk, 1985). However, In the CA1 layer a 68% cell loss was detected (West, Coleman, Flood, & Troncoso, 1994). In contrast, virtually no cell loss in this region occurred in healthy age-matched subjects (West et al., 1994).

In addition to the actual loss of neurons, those cells still surviving undergo a series of degenerative changes in individuals with AD. Neurofibrillary tangles (NFT) and senile plaques (SP) are commonly found in the brains of both healthy elderly individuals and in AD patients, but are much more dense in AD patients (Price, Davis, Morris & White, 1991). SP are comprised of an amyloid core surrounded by swollen degenerating neurites (pre- and post-synaptic nerve terminals) and glial cells, and are generally larger than neurons (Mann, 1988; Perry, 1986). NFTs are accumulations of fibrillary material that originate within neuronal cell bodies. As the neurofibrillary material accumulates within the neuron, it displaces intracellular organelles until the

cell dies, leaving behind a tangle (Saper, 1988). Thus, the NFT and the SP represent the cell bodies and terminal axons, respectively, of neurons that have been affected by the degenerative processes of AD.

The density of SP and NFT in the neocortex and hippocampus at autopsy are markers used to diagnose AD. Guidelines for SP and NFT densities required to merit the diagnose of AD upon autopsy require that SP and NFT be present in the cingulate cortex, hippocampus, entorhinal cortex, amygdala and the association areas of the temporal and frontal cortical lobes (Khachaturian, 1985; Mann, 1988; Saper, 1988).

Neurochemical disturbances in AD occur primarily in the cholinergic system. In addition to the depletion of ACh, norepinepherine concentrations in the neocortex and the hippocampus and serotonin levels in the cortex are reduced, as are serotonin receptor densities (Rossor, 1988). GABA activity is diminished in the temporal cortex and midbrain, and glutamate concentrations and uptake are also decreased (Fowler, O'Neill, Winblad & Cowburn, 1992; Mann, 1988). The loss of cells in the nucleus basalis of Meynert, the locus coeroleus and the raphe nuclei are considered to be the major causes of the reductions of ACh, norepinepherine, and serotonin, respectively (Rossor, 1988; Henderson & Finch, 1989).

Clinical Effects:

According to the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) of the National Institute of Health and the Alzheimer's Disease and Related Disorders Association (ADRDA) criteria (McKhann et al., 1984), in order to receive a diagnosis of probable AD (confirmed as definite AD at post-

mortem), a patient must have deficits in two or more of the following areas of cognition: orientation to place and time, memory, language, praxis, attention, visual perception, problem solving or social functioning. The most common complaint and usually the earliest, and most prominent symptom, is memory impairment (Nebes, 1992). AD patients show a more prominent dysfunction on tasks of long-term rather than short-term explicit memory, including word lists and numbers (Nebes, 1992). Implicit memory is also impaired in AD patients under some circumstances (Brandt, Spencer, McSorley & Folstein, 1988; Salmon, Shimamura, Butters & Smith, 1988), whereas implicit memory generally remains intact in normal aging (Craik, 1994). The primary memory deficit in AD appears to be one of stimulus encoding, rather than storage or retrieval, although storage is somewhat impaired compared to normals (Nebes, 1992; Grosse, Wilson & Fox, 1990).

Women with AD were more impaired on tests of verbal fluency, verbal delayed recall and object naming, and showed a higher rate of forgetting verbal material than men, after controlling for age, education and dementia duration (Henderson & Buckwalter, 1994). Factor analysis of the neuropsychological test scores indicated that women were more impaired on a language factor, but there were no gender differences for the memory and attention factor or the visuospatial factor. These results support those of a previous longitudinal study in which women with AD matched for age, education and severity of dementia performed worse than men on tests of naming and word recognition (Ripich, Petrill, Whitehouse, & Ziol, 1995).

Sex Steroids and AD:

Estrogen and AD:

After the menopause, when estrogen levels decrease substantially, women are at increased risk for AD. Based on the neurobiological evidence reviewed previously, there is reason to believe that estrogen may slow the progression of AD or possibly even help to protect against this devastating illness.

Results of three nonblinded, uncontrolled studies provide suggestive evidence of a beneficial estrogenic effect. Three of seven women with AD treated with 2 mg micronized E_2 daily for six weeks showed improved scores on the Mini-Mental Status Examination (MMSE) and on the Randt Memory Test, while scores of the other four remained unchanged (Fillit, 1986). Similarly, of seven women with AD treated with 1.25 mg CEE daily for six weeks, six showed improvement on the New Screening Test for Dementia, which is not available in English (Honjo et al., 1989). In the third study, 1.25 mg CEE daily was administered to 15 women with AD for six weeks and 15 other women with AD were designated as a control group and not treated. Patients were not randomly assigned to treatment or control. Mini-Mental Status scores of the estrogen treated women increased significantly after administration of E_2, and returned to baseline three weeks after estrogen was withdrawn. No changes in scores occurred in the control subjects over the nine week period (Ohkura, Isse, Akazawa, Hamamoto, Yaoi & Hagino, 1994). Given the uncontrolled nature of these studies and their very small sample sizes, it is difficult to draw any conclusions regarding the efficacy of estrogen for treating AD, despite the generally positive results reported.

Henderson, Watt & Buckwalter (1996) compared 9 women with AD who were

taking ERT at the time of their diagnosis to matched groups of estrogen non-users and to men. The women estrogen-users performed better on the Boston Naming Test than the other two groups. This test of language naming, considered to measure semantic memory, was also more impaired in women AD patients compared to men (Henderson & Buckwalter, 1996). An epidemiological retrospective, case-control analysis was carried out on a community sample of 143 volunteer women who met criteria for probable AD, and on 92 control women (Henderson, Paganini-Hill, Emmanuel, Dunn, & Buckwalter, 1994). Seventy women in the AD group had subsequently died and autopsy confirmed the diagnosis of AD. Estrogen use had been assessed at the time of entry into the study, and was used as the outcome measure. AD patients were significantly less likely than control subjects to use estrogen replacement (7% vs. 18%), when controlling for education and age. Within the AD group, estrogen users had significantly better performance than non-users on the MMSE, although there were no differences between these sub-groups in age, education or symptom duration. Due to the retrospective nature of this study it is impossible to attribute causality to these findings.

The relationship between estrogen use and subsequent AD was investigated in a cohort of 8,877 female residents of a retirement community in southern California who were first assessed for estrogen use by self report in 1981. Of the 2529 females who had died in the intervening years, 138 of those had AD as the cause of death on the death certificate. Four controls were matched according to date of birth and date of death to each AD patient. The risk of AD for estrogen users was about 65% of that

for women who had never used estrogen. The risk decreased with both increasing dose of the longest used oral estrogen and increasing duration of use. Additionally, the risk of AD decreased significantly with decreasing age at menarche and increasing weight, indicators of increased endogenous exposure to estrogens (Paginini-Hill & Henderson, 1994).

Another recent prospective report of 1124 community dwelling women found that the age at onset of AD was significantly later in women who had taken estrogen previously (12.5% of the population) than in those who did not, and the relative risk of the disease was significantly reduced in estrogen-users, after adjusting for education, ethnic origin, age and apolipoprotein-E genotype (Tang et al., 1996). Similarly, 472 post- or peri-menopausal women were followed for 16 years as part of the Baltimore Longitudinal Study of Aging, after which time 34 of the women had developed AD. Of those, only nine were estrogen-users, resulting in a relative risk for AD of 0.46 for estrogen-users compared to non-users, after controlling for education (Kawas et al., 1997).

Not all reports have shown a beneficial effect of estrogen. Using computerized pharmacy data, a more rigorous methodology than self report, Brenner et al. (1994) compared estrogen-use in 107 females with AD with mild to moderate dementia to 120 age matched controls. Subjects were obtained from the AD Patient Registry of the University of Washington, which is based on the enumerated health plan population. There was no difference in the odds ratio of AD in estrogen-users and non-users; roughly 50% of both the cases and the controls had received ERT, yielding an odds

ratio of 1.1, which indicated no association of ERT with AD. In a large case-control study of 130 AD patients and matched controls, an odds ratio of 1.15 for previous estrogen use was reported (Graves et al., 1990). Moreover, similar rates of estrogen use were evident in AD patients and control subjects.

In summary, the generally retrospective nature of these epidemiological studies do not allow for firm conclusions regarding the relationships between estrogen use and AD. However, results of both clinical and, to a lesser extent, epidemiological studies, combined with our knowledge of estrogenic effects in brain areas involved in AD, point to exciting and possibly fruitful avenues for future research.

T and AD:

There are no studies investigating possible relationships between cognition and T levels in AD patients. Neither have their been any reports of whether T levels in AD patients differ from those of age-matched controls.

Cortisol and AD:

Numerous studies of normal aging have shown that cortisol production remains stable with increasing age (Sharma et al., 1989; Sherman et al., 1985; Waltman et al., 1991). However, there have been reports of elevated CRT in AD patients (Leblhuber, et al., 1993; Swaab et al., 1994; Maeda, Tanimoto, Terada, Shintani & Kakigi, 1990). The possibility that a pathological process of HPA dysregulation may cause an increase in cortisol production in AD, a hypothesis proposed by Sapolsky et al. (1986), has recently been investigated by a number of researchers. The administration of DEX, ACTH or corticotrophin releasing hormone (CRH) to AD patients and subsequent

measurement of the response of several HPA markers allows an assessment of the degree to which the HPA axis is reacting to feedback. Studies of this nature have found that higher post-DEX CRT levels in AD were associated with hippocampal atrophy on MRI (O'Brien, Ames, Schweitzer, Colman et al., 1996), that AD patients were more likely to be DEX nonsuppressors (Hatzinger et al., 1995; Nasman, Olsson, Viit & Carlstron, 1995), that CRH administration resulted in hypersecretion of CRT and blunted ACTH response (Nasman et al., 1996) and that ACTH administration caused hypersecretion of CRT (O'Brien, Ames, Schweitzer, Mastwyk & Colman, 1996). These studies all support the notion that the feedback regulation of the HPA axis is disturbed in AD. Only one study found an association between CRT levels and cognitive functions. In a longitudinal investigation of CRT over a one year period in nine men and three women with AD, CRT levels at baseline correlated positively with cognitive deterioration over the next 12 months as assessed by the Alzheimer's Disease Assessment Scale (Weiner, Vobach, Svetlik & Risser, 1994).

DHEAS and AD:

DHEAS is an exclusively adrenal androgen and its production decreases with increasing age. Plasma DHEAS concentrations were lower in AD patients compared to age-matched controls (Sunderland et al., 1989; Yanase et al., 1996). However, other studies have failed to confirm this finding (Leblhuber, Windhager, Reisecker, Steinparz, & Dienstl, 1990; Leblhuber et al., 1993; Cuckle et al., 1990; Spath-Schwalbe, Dodt, Dittmann, Schuttler & Fehm, 1990; Birkenhager-Gillesse, Derksen & Lagaay, 1994). The question of whether AD patients have lower DHEAS levels than

normal controls remains controversial and will be addressed in Study 3.

In the Leblhuber et al. (1993) study of 24 patients with AD, neither levels of DHEAS or CRT were correlated with memory function as assessed by the MMSE, or with the duration of AD symptoms. No other cognitive tests were administered. Sunderland et al. (1989) similarly failed to find correlations between levels of DHEAS and dementia severity or baseline cognitive testing in a sample of 10 AD patients. It is possible that small correlations would not be significant with such small sample sizes. However, DHEAS levels of male nursing home residents were inversely related to the presence of organic brain syndrome (AD, multi-infarct dementia and other types) and to the degree of dependance in activities of daily living (Rudman et al., 1990), suggesting a possible relationship between DHEAS and dementia within a more heterogeneous population.

DHEAS/CRT ratio and AD:

Since DHEAS has antiglucocorticoid properties, the ratio of DHEAS/CRT may serve as a measure of the putative protective actions of DHEAS against the damaging hippocampal effects of CRT (Svec & Lopez-S, 1989). Indeed, a lower DHEAS/CRT ratio occurred in elderly AD patients compared to age-matched controls, particularly in women (Leblhuber et al., 1993). However, the DHEAS/CRT ratio was not correlated with the duration of AD symptoms or with memory function as assessed by the MMSE, which was the only cognitive test administered. DHEAS levels decreased with age in all subjects, resulting in a decrease in the DHEAS/CRT ratio in the more elderly controls. In the female AD patients, even lower ratios of DHEAS/CRT were

found compared to the control women. As well, women with AD had higher absolute CRT levels than the control women and the AD men. Taken together, it appears that high CRT levels may impair memory functions, while DHEAS may counteract the effects of CRT in the healthy elderly and in AD patients, most particularly in women.

Memory Assessment

Traditional Memory Tests:

Traditionally, memory has been assessed using neuropsychological batteries that measure the many different aspects of memory discussed earlier. The Wechsler Memory Scale - Revised (WMS-R; Wechsler, 1987) is a commonly used instrument with several subtests assessing different aspects of explicit memory. The Paragraph Recall tests assesses verbal propositional memory immediately and after a delay component, while the Paired-Associates task assesses a more rote-learning aspect of verbal memory (Ernst, Warner, Morgan, Townes, Eiler, & Coppel, 1986). Visual memory is also assessed by the Figural Memory and Visual Reproduction subtests (Wechsler, 1987). Other traditional memory tests include the Selective Reminding Test (Buschke, 1974), and the test of Category Retrieval which measures aspects of verbal semantic memory, but does not measure explicit memory.

Ecologically valid memory testing:

Although some traditional neuropsychological tests have been shown to correlate reasonably well with lesions to discrete brain areas (for example the Paragraph Recall is a good test of the integrity of the hippocampal memory system), many criticize their lack of ecological validity and question the generalizability of such

test results to real-world functioning. Increasingly, the rationale of memory testing has shifted from associating brain areas with specific memory functions and tests, to predicting functioning in daily life (Cunningham, 1986; Erickson & Howieson, 1986; Ferris, Crook, Flicker, Reisbert, & Bartus, 1986).

Crook and colleagues have developed a battery of computerized everyday memory tests which measure memory for names, faces, object location, telephone numbers and grocery list learning, that have clear ecological validity (Larrabee & Crook, 1992). As well, the Rivermead Behavioural Memory Test (RBMT; Wilson, Cockburn & Baddeley, 1985) is a face valid standardized test that acts as a bridge between laboratory-based measures of memory and assessments obtained by questionnaire and observation (Wilson, Cockburn, Baddeley, & Hiorns, 1989).

Hormones and Mood

Estradiol and Mood:

It is important to consider mood in any study assessing cognitive functioning, as depressed mood is often associated with cognitive deficits (Emery, 1988; Kaszniak & Christenson, 1994; McCallister & Price, 1982). In the elderly, approximately 20% of depressed patients show cognitive deficits severe enough to be labeled "depression related cognitive dysfunction" (LaRue, D'Elia, Clark, Spar & Jarkvik, 1986). A prominent biological theory of depression holds that abnormalities or deficits in central serotonergic function occur in some groups of depressed patients (Lapin & Oxenkrug, 1969; Maes & Meltzer, 1995). An earlier theory, the catecholamine deficiency hypothesis, implied that depression involves an impairment of central adrenergic

functioning (Schildkraut, 1965). MAO degrades both serotonin and norepinepherine in the brain, and has been a target of antidepressant pharmacotherapy in the past.

There is reason to believe that E_2 affects mood in women via its influence on the serotonergic system. Studies of sex differences in the synthesis and turnover of 5-hydroxytryptamine in the hippocampus show that female rats have higher metabolism than males (Haleem et al., 1989). In OVX rats, E_2 reduced serotonin receptor density in areas of the brain known to contain estrogen receptors (Biegon, Rainbow & McEwen, 1982) and increased the rate of degradation of MAO, the enzyme that catabolizes serotonin (Luine et al., 1975). This suggests that E_2 might act to increase the brain concentration of serotonin which, in turn, would enhance mood. In a double-blind, cross-over study of surgically menopausal women, Sherwin & Gelfand (1985) found that hormone replacement therapy was effective in lowering depression scores. This finding was subsequently confirmed in another group of surgically menopausal women (Sherwin, 1988b), where mood was found to covary with circulating levels of E_2 in these generally healthy, non-depressed women. This relationship was extended to naturally postmenopausal women (Sherwin, 1991), where women receiving estrogen reported more positive mood than those receiving both estrogen and progestin. Moreover, ERT in surgically menopausal women not only improved mood compared to placebo, but also increased the number of tritiated imipramine binding sites on platelets (Sherwin & Suranyi-Cadotte, 1990). These binding sites are thought to modulate the presynaptic uptake of serotonin in the brain (Paul, Rehavi, Skolnick, & Goodwin, 1984).

An important point to note is that none of the women in the above studies were suffering from clinical depression and therefore the beneficial estrogenic effects on mood cannot be generalized to women with clinical depression. However, two reports of ERT in clinical depression have hinted that E_2 may even help alleviate symptoms of severe, refractory depression. Crammer (1986) administered combined E_2/T therapy to a 37 year-old woman with recurrent depression associated with the menstrual cycle which seemingly alleviated the depression for eight years. Pharmacological doses of ERT administered for three months to 23 women (15 premenopausal and eight postmenopausal) with severe persistent depression were associated with a decrease in Hamilton Depression Rating Scale scores compared to a placebo, although scores still remained within the depressed range (Klaiber, Broverman, Vogel, & Kobayashi, 1979).

T and Mood:

Treatment of postmenopausal women with either E_2, T or both ameliorated depressive mood symptoms (Sherwin & Gelfand, 1985). Whether this was due to the overall activating effects of T (Rose, 1972), or its aromatization to E_2, is unclear. In depressed men, circulating levels of T were lower than those of non-depressed controls (Rubin et al., 1981), and were reduced relative to the severity of the depression (Yesavage, Davidson, Widrow & Berger, 1985). In clinical trials, T administration was as effective as amitriptyline in alleviating depressive symptoms in men with major depression (Vogel, Klaiber, & Broverman, 1985), and in 64% of 81 men with HIV illness and associated mood problems (Rabkin, Rabkin & Wagner, 1995). Thus, exogenous T treatment seems to have mood-elevating effects in both men and women.

CRT and mood:

Higher CRT levels occur in many individuals with major depressive disorder (Sikes et al., 1989). Depressive patients were more likely to show dysregulation of the HPA axis in the form of nonsuppression of CRT secretion on the DEX suppression test (Wolkowitz, 1994). Twenty-seven asthmatic children receiving high doses of Pregnenolone (61.5 mg/day) evidenced more depressive symptomatology than when they were administered a low dose (3.33 mg/day). Additionally, adolescents with major depression had higher evening CRT levels than matched non-depressed controls (Goodyer, et al., 1996). This research suggests that elevated CRT levels are associated with increased depressed mood in a number of different populations.

DHEAS and mood:

Numerous anecdotal reports from small trials have suggested that DHEAS may be related to mood (for a review, see Wolkowitz et al., 1997). Morning DHEAS levels were lower in a group of depressed adolescents compared to age-matched controls (Goodyer et al., 1996). DHEA administered to healthy elderly individuals resulted in significant increases in self-evaluated ratings of "well-being" (Morales et al., 1994). In a recent clinical trial of DHEAS administration for four weeks to six elderly patients with major depression and low basal plasma DHEAS levels, depression ratings improved significantly pre- to post-treatment, and increases in circulating levels of DHEAS were correlated with decreases in Beck Depression Inventory and Hamilton Depression Rating Scale scores (Wolkowitz et al., 1997). Taken together these results indicate that all four steroid hormones might have influences on mood as well as on

cognition.

In summary overall, although it has been established that certain aspects of memory function decline with aging, and that circulating levels of several hormones also decrease over time and influence these same memory functions and the brain areas underlying them, the possible associations between the changes in levels of steroid hormones and the concomitant decreases in specific cognitive abilities during the normal aging process have not been thoroughly investigated. Nor have the relationships between these hormones and cognition in AD patients been thoroughly evaluated. These studies represent an attempt to investigate possible relationships between cognitive functions, primarily memory, and hormone levels in groups of elderly age-matched healthy men and in women who were either estrogen-users or non-users. The same hypotheses were tested in groups of men and women with AD.

Study 1 - Longitudinal Changes in Hormone Levels and Memory in Healthy Elderly Men, and in Women Estrogen-users and Non-users

Introduction

Based on the research findings that associate E_2, T, CRT, DHEAS and the DHEAS/CRT ratio with memory functioning in animals and humans, this study was undertaken to investigate and further elucidate the relationships between levels of these hormones and specific aspects of memory functioning in healthy elderly men, women estrogen-users and women estrogen non-users. Most previous studies of this nature have investigated either men or women only, and many different instruments have been used to measure aspects of memory. Age comparisons have usually been cross-sectional, and no previous study has longitudinally investigated changes over time in hormone levels and memory functioning in the same population. As well, no other studies have investigated all four steroid hormones and cognitive function in the same individuals.

Hypotheses

Based on the literature review, several hypotheses were proposed: 1) Women estrogen-users would perform better on tests of verbal memory than estrogen non-users, 2) Women estrogen-users would maintain verbal memory test scores over time whereas estrogen non-users would show a temporal decline in scores, 3) Overall, women would outperform men on verbal memory tasks, 4) Men would outperform women on visuo-spatial tasks, 5) Higher T levels would be associated with better performance on visual/spatial tasks in men, 6) Higher E_2 levels would be associated

with better verbal memory performance in estrogen-users and perhaps in men, 7) Men would have higher T and DHEAS levels than women. 8) There would be no group differences in CRT levels. 9) E_2 and T levels would decline over time in the men. 10) E_2 and T levels would remain stable in both groups of women. 11) DHEAS levels would decline in all three groups, but CRT levels would not change significantly. 12) Subjects with higher CRT levels would have lower scores on explicit memory tests than those with lower CRT levels.

Methods

Participants - Time 1

Thirty-one males. 41 female estrogen non-users, and 14 female estrogen-users over the age of 65 were recruited through advertisements in local newspapers. All subjects (Ss) were living independently in the community. Ss experiencing any major acute or chronic medical or psychiatric illnesses were excluded, including those with a history of stroke, recent heart disease, diabetes or vascular disorders, those recently diagnosed with depression, anxiety, dementia or psychotic disorders, and those currently taking any psychotropic medication.

Participants - Time 2

An average of 1.5 years later all the subjects were invited to return to the laboratory for retesting. Twenty-three of the men, 27 of the female estrogen non-users and 10 of the estrogen-users returned for Time 2 testing.

Materials - Time 1

The following test battery was administered to each S once in an individual test

session (Appendix B).

Verbal Memory

Wechsler Memory Scale (WMS, Wechsler, 1945) Paragraph Recall - Immediate and Delayed: The S listened to a short paragraph of about four to five sentences and then was asked to verbally recall what he or she remembered from the passage. Two paragraphs were presented once each. After approximately 30 minutes, the S again repeated all he/she could remember of the paragraphs, which were not presented a second time.

WMS Paired-Associates - Immediate and Delayed: The S listened to a list of 10 word pairs presented in random order, six of which were clearly related (easy-associate; e.g., fruit-apple) and four of which had no apparent relationship (hard-associate; e.g., necktie-cracker). After hearing the list, the S was asked to recall the word that was paired with each cue word. Three such trials of presentation and immediate recall were conducted. After a 30 minute delay, one final recall trial was administered. In scoring, two points were given for a correctly recalled hard-associate and one point for an easy-associate.

Selective Reminding Test (Buschke & Ruld, 1974) - Immediate and Delayed: The S initially read aloud 12 words presented one at a time on cue cards. He/she was then asked to recall all of the words he/she was able. For the remaining five trials, the S was verbally reminded of words not remembered and again asked to recall all of the words. A 7 minute delay component tested free recall and was followed by an auditory forced-choice recognition test of words not recalled. The S

was unaware of the delay component at the initial testing.

Visual Memory

Wechsler Memory Scale - Revised (WMS-R, Wechsler, 1987) Visual Reproduction: The S was shown a design for 10 seconds and was then asked to draw what he/she remembered seeing on the card. Four cards of designs were presented once each. Ss were given separate sheets of paper for each drawing to minimize visual exposure to designs presented earlier.

WMS-R Visual Paired Associates - Immediate and Delayed: The S saw six different designs, each of which was paired with a different color, for three seconds. He/she then saw each design alone, and had to point to the associated color in a separate folder. Errors were corrected by the experimenter. This procedure was repeated for 6 trials or until all six pairs were correctly identified. After a 30 minute delay, the S again saw the designs and had to point to the associated color for each.

WMS-R Figural Memory: The S saw three designs for 15 seconds and was encouraged to remember them. He/she then saw an array of nine designs and had to point out the three just seen. This procedure was repeated with different designs for three trials.

WMS-R Digit Span - Forward and Backward: Forward - The S was read increasingly long groups of numbers and asked to repeat them immediately after hearing each group. For Backwards Digit Span, the S was read increasingly long groups of numbers and asked to repeat them backwards.

WMS-R Visual Memory Span - Forward and Backward: Forward - The

S watched as the experimenter touched a series of colored squares on a card, and was asked to touch them in the same order immediately afterwards. Backward - The S watched the experimenter touch a series of colored squares on a different card and had to touch them in the reverse order immediately afterwards.

Language Fluency / Semantic Memory

Category Retrieval (Drachman & Leavitt, 1972): The S listed aloud as many items as possible that belonged to a certain category in a 60 second period. The five categories used were: animals, clothing, fruits, first names, and vegetables.

Mood Questionnaires (Appendix C)

Beck Depression Inventory (BDI; Beck, Ward, Mendelson, Mock & Ergaugh, 1961): The S read several groups of statements describing common depressive symptoms and checked off the one statement from each group that best described the way he/she had been feeling over the last week.

Geriatric Depression Scale (GDS; Yesavage et al., 1983): The S read 30 statements describing depressive symptomatology and indicated (yes or no) whether the statement applied to the way they had been feeling over the past week.

Profile of Mood States - Bipolar Form (POMS-BI; Lorr & McNair, 1982): The S indicated for each of 72 adjectives whether they had felt "much unlike this", "slightly unlike this", "slightly like this", or "much like this" over the past week. This scale yields scores on six dimensions of mood: elated-depressed, clearheaded-confused, energetic-tired, composed-anxious, confident-unsure, and agreeable-hostile. Each mood state appears on a bipolar scale, with negative numbers representing the negative affect

pole and positive numbers representing the positive affect pole. Scores can range from -18 to 18 on each subscale. These scales are more sensitive to small mood fluctuations than the BDI or the GDS.

Multiple Affect Adjective Checklist - Revised (MAACL-R; Zuckerman & Lubin, 1985): The S indicated which of 132 adjectives best reflected his/her present mood state at the time of testing. This instrument yields scores for current levels of anxiety, depression, hostility, positive affect, and sensation-seeking.

Materials - Time 2

The same test battery as in Time 1 was re-administered, with the exception of the MAACL-R and the BDI, which were eliminated as redundant with the POMS and GDS and in order to shorten the test battery.

Rivermead Behavioural Memory Test:

The Rivermead Behavioural Memory Test (RBMT; Wilson et al., 1985), an ecologically valid test of everyday memory functioning, was added at T2. Scores on the RBMT show high inter-rater reliability and good criterion validity, and correlate highly with behavioural observations of memory lapses. Scores also correlate significantly with some traditional neuropsychological test scores (Wilson et al, 1989). The RBMT is composed of the following subtests:

Name: At the beginning of the test, the S was shown a picture of a woman and told that her name was Catherine Taylor. After approximately 1/2 hour, at the end of the test, the S was shown the picture again and asked the woman's name. If no spontaneous response was produced, the initials of the woman were given as a prompt.

Belonging: At the beginning of the test, the S was asked for a personal object, such as a handkerchief or glasses case, and the experimenter put it away in a drawer, telling the S to remember to ask for the object at the end of the test, specify what it was and where it was put. If the S did not ask spontaneously, the experimenter provided a prompt.

Appointment / Results: Near the beginning of the test, a timer was set to beep in 20 minutes. The S was told to remember to ask when they would receive the results of the test when the alarm beeped. Another version of the task was for the S to ask when their next appointment is. However, this question was not appropriate for these Ss, but was used in Study 2.

Picture Recognition: Ten line drawings of common objects were presented for five seconds each. The S was told to name the object and try to remember it. Approximately 10 minutes later, 20 drawings were shown including the ten originals which the S was asked to identify. False positives were subtracted from correct choices to determine the score.

Face Recognition: Five faces were shown for five seconds each and the S was told to try to remember them. Approximately 10 minutes later, ten faces were shown including the five originals which the S was asked to identify. Scoring was the same as for Picture Recognition.

Story (Immediate and Delayed): A short story was read to the S who was asked to repeat it immediately and then, again, after a delay of approximately 15 minutes.

Route (Immediate and Delayed): The experimenter told the S to watch what they did and then do the same thing when they were finished. She then walked from one location to another in the room making five distinct stops and returned to her chair. The S was asked to trace the same route around the room as the experimenter had taken. Approximately 15 minutes later, the S was asked to repeat the route (delayed).

Message (Immediate and Delayed): When the experimenter got up to demonstrate the route, she took an envelope marked "message" with her, and deposited it on a counter at stop three of the route. The S was told to do the exact same thing as the experimenter and scored as to whether the message was picked up spontaneously and left in the correct location.

Orientation: Nine orientation questions assessed orientation to time, place, and current events.

Date: The Date was scored separately from the other orientation questions as it is considered a more significant prognostic index.

Total Score (out of 24): Each subtest was allocated a standardized two points. Ss could earn either 0, 1 or 2 points on each subtest by performing to set levels. The standardized scores were added to achieve the total score.

Plasma Hormone Assays:

Ten millilitres of blood were collected via venipuncture into heparinized Vacutainer tubes at each test session. The blood was immediately centrifuged and the plasma stored at -50 degrees C. All samples were analyzed by radioimmunoassay at

the conclusion of each phase of the study. E_2 was measured using the Clinical Assay for the Direct Determination of 17 beta-E_2 in Human Serum or Plasma kit (Sorin Biomedica, Saluggia, Italy). Free T was assayed by means of the Coat-A-Count Free T procedure (diagnostic Products Corporation, Los Angeles, CA); DHEAS was analyzed using the Radioimmunoassay Kit for the Quantitative measurement of DHEAS in Serum or Plasma (Diagnostic Systems Laboratories Incorporated, Webster, Texas), and CRT by the Clinical Assays GammaCoat CRT I-RIA Kit (Incstar Corporation, Stillwater, Minnesota).

Procedure - Time 1:

Prospective subjects who replied to newspaper advertisements were screened over the phone for current medication use and medical history before being scheduled for an interview (Appendix A). Ss then reported to the laboratory individually, females at 10h00, males at 12h30, and signed a consent form approved by the McGill University Ethics Committee (Appendix A). Female Ss had their blood samples taken by a registered nurse after their test session whereas the male Ss had their samples taken before their neuropsychological test session. This was done in order to control for the time of day that the blood sample was taken and in view of the constraints on the availability of the blood technician. For all Ss, therefore, the blood sample was obtained between 12h00 and 13h00 on the day of testing.

Test sessions were carried out in the laboratory and each lasted 1.5 to 2 hours. Ss first completed a general information form that provided sociodemographic information as well as personal, medical, psychological, educational and vocational

history (Appendix A). Next, the test battery was administered. Each S was paid $15 at the end of the session to compensate them for their transportation expenses.

Procedure - Time 2:

Ss were telephoned an average of 1.5 years after their first test session, and invited to return to the laboratory for a second test session and another blood sample. They were screened over the telephone for any changes in their medical status during the interval, and any who were experiencing any major acute or chronic medical or psychiatric illnesses were excluded, including those with a history of stroke, recent heart disease, diabetes or vascular disorders, those recently diagnosed with depression, anxiety, dementia or psychotic disorders, and those currently taking any psychotropic medication. Ss who met the exclusion criteria and agreed to return were scheduled for testing. The same procedure was followed as for T1, with the exception that the test battery took somewhat longer with the addition of the RBMT, and Ss were compensated $20 for their travel and parking expenses.

Results

Participants - Time 1 and 2:

Demographic characteristics of the Ss are presented in Table 1. Although the mean socioeconomic status score indicated that most of the Ss were middle class (Blishen, 1967), at T1 one-way ANOVA analysis with Bonferroni corrected post-hoc t-tests indicated that the female estrogen-users were of significantly higher socioeconomic status ($F[2,83]=4.17$, $p<.05$) and had more years of formal education ($F[2,83]=3.57$, $p<.05$) than female non-users. There were no differences in age between the three

Table 1
Sociodemographic Characteristics - Healthy Elderly

Group		Age (years)		Education (years)		Socioeconomic Status^	
		Mean	SD	Mean	SD	Mean	SD
Men	T1 (n=31)	71.9	5.9	12.1	3.5	55.5	11.9
	T2 (n=23)	73.4	5.9	12.8	3.6	55.9	12.7
Female estrogen non-users	T1 (n=41)	72.4	5.7	11.9	2.9	52.7	13.3
	T2 (n=27)	73.5	5.0	12.0	3.0	53.1	15.0
Female estrogen-users	T1 (n=14)	71.2	4.9	14.4*	2.7	63.6*	8.78
	T2 (n=10)	73.5	4.9	14.8	2.3	63.1	10.2
Total sample	T1 (n=86)	72.1	5.6	12.4	3.1	55.4	12.6
	T2 (n=60)	73.4	5.3	12.8	3.3	55.8	13.7

* Time 1: Female E-users higher then Female E non-users only ($p<.05$).
Time 2: No group differences
^ Socioeconomic Status as measured by Blishen (1967).

groups, who were, on average, 72.1 years old. At T2, there were no significant differences between the three groups in age, SES or education. This was due primarily to the fact that there were smaller numbers of Ss at T2, and because of slight shifts in the group means of the Ss who returned.

Details of estrogen use and menopausal history of the women estrogen-users are presented in Table 2. Of the 14 women using estrogen, 9 had undergone hysterectomy and bilateral salpingo-oophorectomy 12-32 years previously (mean 21.7 years) and 7 had been taking estrogen replacement therapy continuously since the surgery. Seven were taking conjugated equine estrogen 0.625 mg daily (CEE; Premarin, Wyeth-Ayerst Laboratories, Canada), two took CEE 0.30 mg daily, and one women was taking 0.625 mg esterified estrogens daily (Neo-Estrone, Neolab Inc.,

Montreal, Canada). The remaining five women had had a natural menopause 16 to 34 years previously (mean = 23 years) and had been taking estrogen for an average of

Table 2
Characteristics of Estrogen Use - Healthy Elderly

Subject Number	Type of menopause	Years since menopause	Estrogen Type + Dose /day	Progesterone Type + Dose /day	Years of treatment
106~	surgical	28	CEE* .625 mg	none	28
130~	surgical	23	CEE .625 mg	none	23
140~	surgical	14	CEE .30 mg	none	14
153~	natural	34	CEE .625 mg	none	34
159	surgical	12	CEE .625 mg	none	12
163~	surgical	32	CEE .625 mg (erratic)	none	32
166	surgical	28	CEE .625 mg	none	28
180~	natural	17	CEE .625 mg	none	9
182~	natural	16	CEE .625 mg	MPA** 2.5 mg	16
183~	natural	23	CEE .625 mg	MPA 2.5 mg	2
184~	surgical	20	CEE .30 mg	none	13
185~	natural	25	CEE .625 mg	MPA 2.5 mg	25
187	surgical	25	CEE .30 mg	none	25
188	surgical	13	Esterified estrogen .625 mg	none	7
Mean Values	natural	23.0			17.20
	surgical	21.67			20.22
	All E users	22.14			19.14

* CEE= Conjugated equine estrogen
** MPA= medroxyprogesterone acetate
~ Returned at Time 2

17.2 years. Three of the naturally menopausal women were taking 2.5 mg of medroxyprogesterone acetate (MPA: Provera, Upjohn Co., Canada) in combination with CEE 0.625 mg daily.

At T2, all five of the naturally menopausal estrogen group returned, and all had continued their hormone regimen (3 taking combined CEE 0.625 mg and MPA 2.5 mg daily; 2 taking CEE 0.625 mg/day only). Of the five surgically menopausal women who returned, three were taking CEE 0.625 mg/day and two were taking CEE 0.30 mg/day, the same doses as at T1. None of the five were taking progestins.

Hormonal Assays - Time 1:

Radioimmunoassays of plasma E_2, free T, CRT and DHEAS were conducted in duplicate for 75 Ss (Women estrogen-users, n=13; Women estrogen non-users, n=38; Men, n=24). Blood hormone levels were not available for all Ss due to problems obtaining samples via venipuncture from some of these elderly Ss. The value reported for each S is the mean of two assays per hormone, both conducted on blood from the same sample. As the distributions of values for CRT was significantly positively skewed, a square root transformation was conducted and subsequent correlational analyses performed on the transformed values. The ratio of DHEAS to CRT was calculated by converting the CRT measurements to the same units as DHEAS, then dividing the CRT values into the DHEAS values for each S. Transformed values of CRT could not be used in these ratios as they would be meaningless in this context. The resulting ratios conformed to a normal curve. These ratios (expressed in exponential notation), and mean absolute hormone values for each

group of subjects appear in Table 3

Table 3
Hormone Levels T1 and T2 - Healthy Elderly

Group			E2 (pmol/L)	T (pmol/L)	CRT (nmol/L)	DHEAS (umol/L)	DHEAS/CRT
Men (M)	T1 (n=24)	Mean	74.4[b]	34.8[e]	325.0	3.0[g]	9.06 E-6[i]
		SD	19.4	8.0	78.1	2.0	4.75 E-6
	T2 (n=22)	Mean	66.1[d,k]	34.1[f]	382.7	3.4[h]	9.89 E-6[j]
		SD	22.2	12.1	123.2	1.9	5.79 E-6
Female Estrogen non-users (FnoE)	T1 (n=38)	Mean	28.0	1.8	289.0	1.6	5.73 E-6
		SD	13.6	1.6	76.2	1.0	3.10 E-6
	T2 (n=23)	Mean	29.3	2.39	359.8l	1.7	5.13 E-6[m]
		SD	15.9	1.89	104.0	1.0	2.75 E-6
female estrogen-users (FE)	T1 (n=13)	Mean	115.6[a]	0.8	304.3	1.5	7.20 E-6
		SD	62.6	0.6	139.3	1.4	6.61 E-6
	T2 (n=10)	Mean	98.2[c]	0.6	306.1	1.1	4.33 E-6
		SD	79.4	0.5	169.0	0.6	3.39 E-6

E_2
a FE > M, FnoE
b M > FnoE
c FE > FnoE
d Men > FnoE

DHEAS/CRT:
i M > FnoE
j M > Both Female Groups

T, DHEAS
e, f M > FE, FnoE
g, h M > FE, FnoE

Changes:
k Men: T1 E_2 > T2 E_2
l FnoE: T1 CRT < T2 CRT
m FnoE: T1 DHEAS/CRT > T2 DHEAS/CRT

Analysis with one-way ANOVA procedures indicated there was a main effect between groups for E_2 levels at T1 ($F[2,72]=48.6$, $p<.001$). When probed with Bonferroni corrected post-hoc t-test analyses, plasma E_2 levels were significantly higher in the female estrogen-users compared to the estrogen non-users and the men ($p<.05$). Also, the men had higher E_2 values than the estrogen non-using women

($p<.05$). As expected, the T levels at T1 were different between the three groups ($F[2,72]=411.2$, $p<.001$), with higher levels in the male group compared to both female groups ($p<.05$), while mean values of T of the female groups did not differ from each other. CRT levels were not significantly different between any of the groups. However, DHEAS levels did differ ($F[2,72]=8.13$, $p<.001$), with higher levels in the male group compared to values of both female groups ($p<.05$). Consequently the DHEAS/CRT ratio was also different between the three groups ($F[2,72]=4.28$, $p<.05$), with higher ratios in the males than in the female estrogen non-users ($p<.05$).

Hormonal Assays - Time 2

Radioimmunoassays of plasma E_2, free T, CRT and DHEAS were again conducted in duplicate for all returning Ss (Women estrogen-users, n=10; Women estrogen non-users, n=23; Men, n=22). Once again, blood hormone levels were not available for all Ss due to problems obtaining samples via venipuncture in one man and four estrogen non-using women. The value reported for each S is the mean of two assays per hormone, both conducted on blood from the same sample. This time, the distributions of values for CRT or any other hormone were not significantly positively skewed, and thus no transformations of the raw data were necessary. The ratio of DHEAS to CRT was calculated as at T1. These values are also presented in Table 3.

Analysis with one-way ANOVA procedures indicated there was a main effect between groups for E_2 levels ($F[2, 52]=12.81$, $p<.001$). Bonferroni corrected post-hoc t-test analyses showed that plasma E_2 levels were significantly higher in the female estrogen-users than in the estrogen non-users ($p<.05$), and the men had higher E_2

values than the estrogen non-using women ($p<.05$). As at T1, the T ($F[2,52]=109.54$, $p<.001$) and DHEAS ($F[2,52]=12.15$, $p<.001$) levels were different between the three groups, with higher T and DHEAS levels in the male group compared to both female groups ($p<.05$), while mean values of T and DHEAS of the female groups did not differ significantly from each other. CRT levels were not significantly different between any of the groups. Because the men had higher DHEAS, the DHEAS/CRT ratio was also different between the three groups ($F[2,52]=8.67$, $p<.001$), with higher ratios in the males than in both female groups ($p<.05$).

Normal values for hormone levels by sex and age are those used by the Endocrine Laboratory of the university teaching hospital that assayed these samples and are presented in Table 4.

Table 4
Hormone Norms

	Men	Women
E2 (pmol/L)	37 - 220	Early Follicular: 110 - 440 Later Follicular: 370 - 1400 Menopause: <100
T (pmol/L)	9.5 - 91.4	0.2 - 8.5
CRT (nmol/L)	08h00: 140 - 690 16h00: 55 - 360	
DHEAS (umol/L)	5.4 - 9.1	Cycling: 2.2 - 9.2 Menopause: 0.3 - 1.6

At T1, the E_2 levels of the female estrogen-users were within the range of the early follicular phase values of the cycle in reproductive-aged women, while the non-users had E_2 levels within the postmenopausal range as expected. However, at T2 the E_2 values of the estrogen-users were slightly lower and the levels of the non-users

remained similarly depressed as at T1. The E_2 levels of the men were in the lower half of the normal range of male values at both T1 and T2. At both test times, the T levels of these 72 year-old men were in the lower third of the normal range of male values, and both groups of women had plasma T levels in the low end of the female range. DHEAS levels in the men were below the lower limit of the normal male range, and DHEAS values were within the postmenopausal range for estrogen-using women at both test times, but slightly higher than the normal menopausal range in estrogen non-users at T2. Also, CRT levels of all three groups, obtained at approximately 12h00, fell between the normal range of 8h00 and 16h00 norms for this hormone known to have a prominent diurnal variation.

Changes in Hormone Levels:

Matched group t-tests with Bonferroni corrections comparing the levels of each hormone in each of the three groups indicated that none of the hormones had changed significantly during the 1.5 year interval in the estrogen-using women. However, in the men, E_2 levels decreased significantly over the interval ($p<.001$), and in the estrogen non-using women CRT levels increased significantly ($p<.001$), and consequently the ratio of DHEAS/CRT decreased somewhat from T1 to T2 in these women ($p<.05$), although this change did not meet the conservative criteria of $p<.01$.

Neuropsychological Tests - Time 1

In order to control for the possible confounding effects of higher SES scores and more years of education in the estrogen-using women compared to the non-users, ANCOVA analyses were performed on neuropsychological test scores

using SES and years of education as covariates. Significant main effects were probed using Bonferroni corrected post-hoc t-tests on the adjusted means. Repeated measures ANCOVA analyses on the Immediate and Delayed components of Paragraph Recall, Paired Associates, Selective Reminding, and Visual Paired Associates failed to find interactions between group and time (Immediate versus Delayed).

As seen in Table 5, there was a main effect of group on Forward Digit Span ($\underline{F}[2,57]=9.03$, $p<.001$) and on Total Digit Span ($\underline{F}[2,57]=5.05$, $p<.01$) such that both the males and the female estrogen-users had higher scores than the estrogen non-users. On the Backward Digit Span, only the estrogen-users scored significantly higher than the non-users ($\underline{F}[2,57]=3.19$, $p<.05$). Additionally, both groups of women scored higher than the men on the Category Retrieval test ($\underline{F}[2,57]=4.88$, $p<.01$).

Pearson product-moment correlations were calculated between test scores and hormone levels for each group (Tables 6 through 10). In order to provide some control for the number of correlations performed, a cut-off value for significance of $p<.01$ was used for all correlations. There were no significant correlations between E_2 levels and any of the test scores in any of the groups (Table 6). T levels were positively correlated with Delayed Paragraph Recall ($\underline{r}=.681$) and Category Retrieval scores ($\underline{r}=.690$) in the estrogen-using women (Table 7). Transformed CRT levels were positively correlated with Digit Span in the men ($\underline{r}=.540$, Table 8), but showed no significant association with test scores of either group of women.

Table 5

Neuropsychological Test Scores - Healthy Elderly

Test Name	Maximum Possible Score	Men		Female Estrogen Non-Users		Female Estrogen-Users	
		T1	T2	T1	T2	T1	T2
Paragraph Recall - Immediate	46	17.68	19.89	18.37	17.29	20.89	20.80
Paragraph Recall - Delayed[a]	46	12.76	16.09	13.76	13.10	17.36	14.20
Paired Associates - Immediate[i]	42	28.45	26.74	27.56	25.30	29.64	28.10
Paired Associates - Delayed	14	10.90	9.96	10.32	9.96	11.21	11.20
Selective Reminding Test - Immediate	72	51.42	48.3	51.71	51.37	52.86	54.22
Selective Reminding Test - Delayed[j]	12	7.42	6.96	7.56	7.33	7.64	10.00[e]
Visual Paired Associates - Imm.	18	11.06	11.35	11.34	12.42	12.29	14.3
Visual Paired Associates - Del.	6	4.35	4.68	4.54	4.96	5.43	5.60
Visual Reproduction[k]	41	29.71	32.24	29.44	33.40	32.50	33.50
Figural Memory	10	6.87	7.10	6.46	6.59	6.21	7.70
Digit Span Total	24	16.26	16.73	13.95[a]	14.07[f]	17.64	17.2
Forward	12	9.42	9.68	7.61[b]	7.70[g]	9.64	10.00
Backward	12	6.84	7.18	6.22[c]	6.59	8.00	8.20
Visual Memory Span	24	15.61	15.74	14.83	14.59	14.14	14.90
Forward	12	8.13	8.39	7.80	7.93	7.57	8.10
Backward	12	7.48	7.35	7.00	6.67	6.57	6.80
Category Retrieval[l]	no max.	83.90[d]	87.65	95.90	90.04	98.71	98.78

Table 5 (con'd) - Legend

Time 1:	a, b	Female E-users and Men > Female E non-users (a, $p<.01$; b, $p<.001$)
	c	Female E-users > Female E non-users ($p<.05$)
	d	Both Female groups > Men ($p<.01$)
Time 2:	e	Female E-users > Men, Female E non-users ($p<.05$)
	f	Men > Female E non-users ($p<.02$)
	g	Men, Female E users > Female E non-users ($p<.005$)
Changes:	h	Interaction: Men increased, Female E-users decrease ($p<.005$)
	i	Main effect of time: T1>T2 ($p<.01$)
	j	Interaction: Female E-users increase, men decrease ($p<.05$)
	k	Main effect of time: T1<T2 ($p<.005$)
	l	Main effect of time: T1>T2 ($p<.05$)

DHEAS levels were negatively associated with performance on Total Digit Span (r=.-.451) and Forward Digit Span (r=-.488) in the estrogen non-using women (Table 9). Finally, a similar pattern of negative correlations was found between the DHEAS/CRT ratio and test performance in the estrogen non-using women (Table 10), such that higher DHEAS/CRT ratios were associated with poorer performance on Total (r=-.519) and Forward (r=-.564) Digit Span and Immediate Selective Reminding (r=-.422) in estrogen non-using women.

To examine whether the effects of combined estrogen-progesterone treatment differentially affected these findings, these analyses were repeated excluding the three estrogen-using women who were also taking progestins. There was no change in any of the neuropsychological test results.

To determine whether duration of estrogen treatment was related to performance on any of the neuropsychological tests, years of estrogen use was correlated with test scores for the estrogen-users. No correlations were significant at $p<.01$.

Table 6

Correlations Between Estradiol Levels and Test Scores - Healthy Elderly

Test Name	Group					
	Men		Female Estrogen Non-Users		Female Estrogen-Users	
	T1	T2	T1	T2	T1	T2
Paragraph Recall - Immediate	.012	.086	-.225	-.188	.315	.018
Paragraph Recall - Delayed	.377	.224	-.005	-.255	.232	-.082
Paired Associates - Immediate	-.068	-.280	-.010	-.126	-.104	.426
Paired Associates - Delayed	.179	-.383	-.182	-.012	-.143	.189
Selective Reminding - Immediate	-.201	-.106	-.208	.068	-.479	-.366
Selective Reminding - Delayed	-.211	-.031	-.005	-.336	-.264	-.637
Visual Paired Associates - Imm	-.078	-.028	.162	-.115	-129	-.133
Visual Paired Associates - Delayed	-.360	.253	-.072	-.179	.138	-.269
Visual Reproduction	-.209	-.199	-.173	-.330	.377	-.237
Figural Memory	-.268	-.035	-.114	.269	-.324	-.059
Digit Span Total	.197	-.043	-.306	-.230	.060	-.299
Forward	.057	.012	-.337	-.306	.083	-.403
Backward	.261	-.199	-.233	.048	.030	-.369
Visual Memory Span	-.066	.032	-.079	-.086	.612	.315
Forward	-.090	.016	-.158	.127	.606	.245
Backward	.001	.040	-.059	-.207	.440	.212
Category Retrieval	-.212	-.113	-.260	-.248	-.142	-.231

Table 7

Correlations Between Testosterone Levels and Test Scores - Healthy Elderly

Test Name	Group					
	Men		Female Estrogen Non-Users		Female Estrogen-Users	
	T1	T2	T1	T2	T1	T2
Paragraph Recall - Immediate	.050	.175	-.086	.035	.510	.197
Paragraph Recall - Delayed	.135	.080	.088	.306	.681*	.183
Paired Associates - Immediate	-.120	-.191	.292	.174	.500	-.299
Paired Associates - Delayed	.186	-.405	.072	.301	.324	-.100
Selective Reminding - Immediate	.172	-.072	-.206	.125	.470	.098
Selective Reminding - Delayed	-.082	-.212	.013	.091	.359	.237
Visual Paired Associates - Immediate	-.310	.497	.307	.413	.345	.615
Visual Paired Associates - Delayed	.027	.149	.219	.372	.282	.350
Visual Reproduction	-.002	.352	-.016	.236	.357	.196
Figural Memory	-.117	.043	.098	-.117	.291	.583
Digit Span Total	-.059	.362	-.169	.276	.195	-.021
Forward	-.082	.073	-.241	-.103	.161	-.052
Backward	-.025	.347	-.038	.394	.206	-.051
Visual Memory Span	.011	.180	-.090	.163	.432	.349
Forward	-.010	.033	-.190	.082	.427	.429
Backward	.031	.286	.023	.170	.302	.013
Category Retrieval	.047	-.038	-.068	.324	.690*	-.221

* $p<.01$

Table 8

Correlations Between Cortisol Levels and Test Scores - Healthy Elderly

Test Name	Group					
	Men		Female Estrogen Non-Users		Female Estrogen-Users	
	T1	T2	T1	T2	T1	T2
Paragraph Recall - Immediate	.124	-.060	-.195	-.290	.038	-.026
Paragraph Recall - Delayed	.220	-.173	-.180	-.271	.238	.129
Paired Associates - Immediate	.183	-.196	.133	-.517	.091	-.151
Paired Associates - Delayed	.051	-.074	.041	-.431	-.063	-.489
Selective Reminding - Immediate	-.034	-.002	.097	-.080	-.090	-.169
Selective Reminding - Delayed	-.278	-.079	-.023	-.476	.122	-.811
Visual Paired Associates - Imm	-.183	.245	.139	-.235	-.247	-.368
Visual Paired Associates - Delayed	-.252	.063	.125	-.145	-.011	-.450
Visual Reproduction	-.080	-.097	.067	-.127	.491	-.052
Figural Memory	-.378	-.188	-.118	.080	-.067	.145
Digit Span Total	.540*	.439	.031	.106	-.626	-.002
Forward	.455	.330	.087	.145	-.297	.069
Backward	.504	.496	.018	.002	-.560	-.016
Visual Memory Span	-.013	.120	.072	-.136	.485	.199
Forward	-.048	.111	.052	.033	.433	.223
Backward	.052	.098	.063	-.209	.426	.037
Category Retrieval	.154	.050	.149	-.392	.069	-.268

* $p<.005$

Table 9

Correlations Between DHEAS Levels and Test Scores - Healthy Elderly

Test Name	Group					
	Men		Female Estrogen Non-Users		Female Estrogen-Users	
	T1	T2	T1	T2	T1	T2
Paragraph Recall - Immediate	-.371	.176	-.242	-.343	-.343	.311
Paragraph Recall - Delayed	-.001	.012	-.124	-.352	-.084	.335
Paired Associates - Immediate	.303	.126	.170	-.238	-.253	-.114
Paired Associates - Delayed	.158	-.108	.106	-.197	-.037	-.162
Selective Reminding - Immediate	.433	.020	-.360	-.398	-.094	.404
Selective Reminding - Delayed	.112	-.141	-.279	-.471	.150	.093
Visual Paired Associates - Imm	-.224	.117	.051	-.296	.234	.479
Visual Paired Associates - Delayed	-.055	.072	-.055	-.334	.169	.069
Visual Reproduction	-.400	.072	-.349	-.328	.529	.204
Figural Memory	-.171	-.148	-.104	-.043	.137	.656
Digit Span Total	.349	.168	-.451*	-.418	-.059	.023
Forward	.355	.082	-.488*	-.401	.030	-.130
Backward	.257	.167	-.299	-.335	-.137	-.003
Visual Memory Span	.068	-.115	-.277	-.529*	.119	.135
Forward	.089	-.199	-.147	-.505	-.104	.395
Backward	.004	.003	-.289	-.385	-.376	-.317
Category Retrieval	.332	.340	-.267	-.500	-.346	-.085

* $p<.01$

Table 10

Correlations Between DHEAS/CRT Ratio and Test Scores - Healthy Elderly

Test Name	Group					
	Men		Female Estrogen Non-Users		Female Estrogen-Users	
	T1	T2	T1	T2	T1	T2
Paragraph Recall - Immediate	.369	.081	-.145	-.197	-.170	.447
Paragraph Recall - Delayed	-.056	.084	-.075	-.206	.002	.300
Paired Associates - Immediate	.358	.162	.099	.071	.085	.214
Paired Associates - Delayed	.101	-.112	.067	.139	.145	.242
Selective Reminding - Immediate	.423	-.024	-.422*	-.287	.116	.425
Selective Reminding - Delayed	.115	-.030	-.347	-.194	.141	.438
Visual Paired Associates - Imm	-.176	-.067	.020	-.076	.331	.591
Visual Paired Associates - Delayed	.023	.035	-.082	-.205	.330	.307
Visual Reproduction	.095	.022	-.354	-.220	-.038	.387
Figural Memory	-.023	-.061	-.054	-.085	-.134	.342
Digit Span Total	.195	-.124	-.519**	-.407	.054	.134
Forward	.250	-.115	-.564**	-.425	.020	-.071
Backward	.101	-.182	-.340	-.286	.080	.067
Visual Memory Span	.139	-.073	-.283	-.455	-.379	-.119
Forward	.167	-.163	-.122	-.520	-.514	.124
Backward	.026	.040	-.315	-.276	-.093	-.384
Category Retrieval	.328	.167	-.303	-206	-.125	.250

* p<.01

** p<.001

Neuropsychological Tests - Time 2:

To ensure that the Ss who returned at T2 were a representative subsample of the T1 Ss, the T1 test scores of all T2 Ss were compared with the T1 scores of those Ss who did not return, using independent samples t-tests. There were no differences in any of the T1 test scores between the returnees and the non-returnees. At T2, similar group differences were found with one-way ANOVA procedures on the Total and Forward Digit Span tests, in that the men scored better than the estrogen non-users on Total Digits ($F[2,57]=4.42$, $p<.05$), and both the men and estrogen-users performed better on Forward Digits ($F[2,57]=6.72$, $p<.005$). This time, scores on Category Retrieval were not significantly different among the groups, but Delayed Selective Reminding Test scores were higher for estrogen-using women compared to both men and estrogen non-using women ($F[2,57]=4.08$, $p<.05$).

Pearson product-moment correlations were calculated between test scores and hormone levels for each group at T2 (also in Tables 6 through 10). Again, in order to provide some control for the number of correlations performed, a cut-off value for significance of $p<.01$ was used for all correlations. There were no significant correlations between E_2 levels and any of the neuropsychological tests (Table 6), nor were any correlations found between T levels and test scores in any of the three groups (Table 7). Neither were significant correlations found between CRT levels and test scores. However, DHEAS levels were negatively associated with Visual Memory Span in female estrogen non-users ($r=-.529$). Finally, there were no significant correlations between the ratio of DHEAS/CRT and any of the test scores at T2.

To determine whether duration of estrogen treatment was related to performance on any of the neuropsychological tests, years of estrogen use was correlated with test scores for the estrogen-users. As at T1, no correlations were significant at $p<.01$.

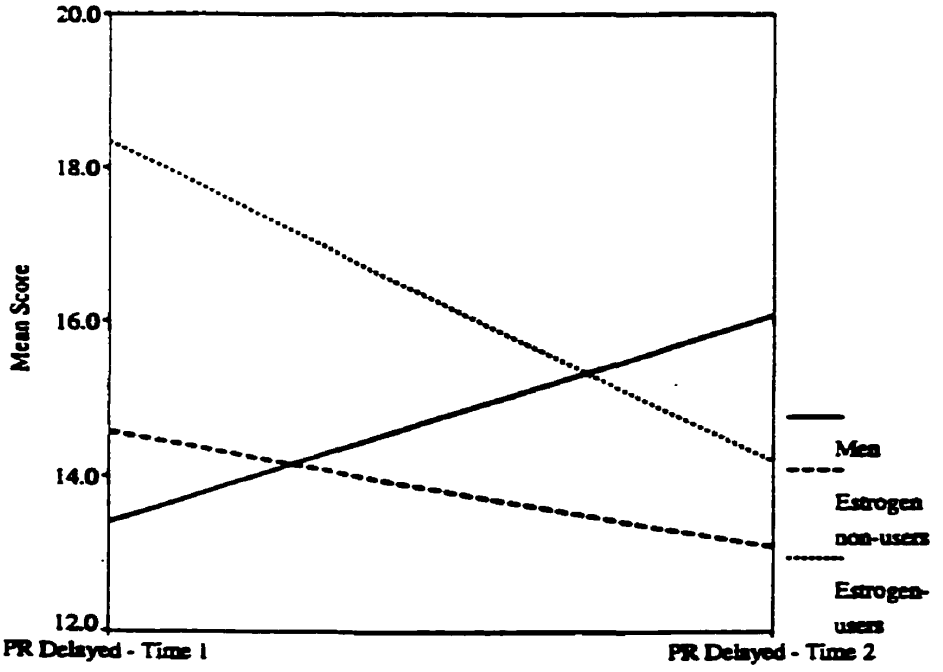
Changes in Neuropsychological Test Scores:

Repeated-measures ANOVAs were calculated to reveal any changes in neuropsychological test scores that occurred over time among the three groups. There was an interaction between group and time on Delayed Paragraph Recall scores ($F[2,56]=5.86$, $p<.005$), and on Delayed Selective Reminding scores ($F[2,55]=3.43$, $p<.05$), but no main effects in either case, which are illustrated in Figures 1 and 2, respectively.

As seen in Figure 1, Delayed Paragraph Recall scores increased over time in the men but decreased in the estrogen-users, causing the interaction. On Delayed Selective Reminding (Figure 2), the opposite pattern was seen, in that scores increased over time in the estrogen-users but decreased in the men and estrogen non-users. There were main effects for time on Immediate Paired Associates ($F[1,57]=7.27$, $p<.01$) and Category Retrieval ($F[1,56]=4.36$, $p<.05$) such that scores decreased in all groups from T1 to T2 as seen in Figures 3 and 4. Scores increased over time across groups on Visual Reproduction ($F[1,51]=10.46$, $p=.002$), illustrated in Figure 5.

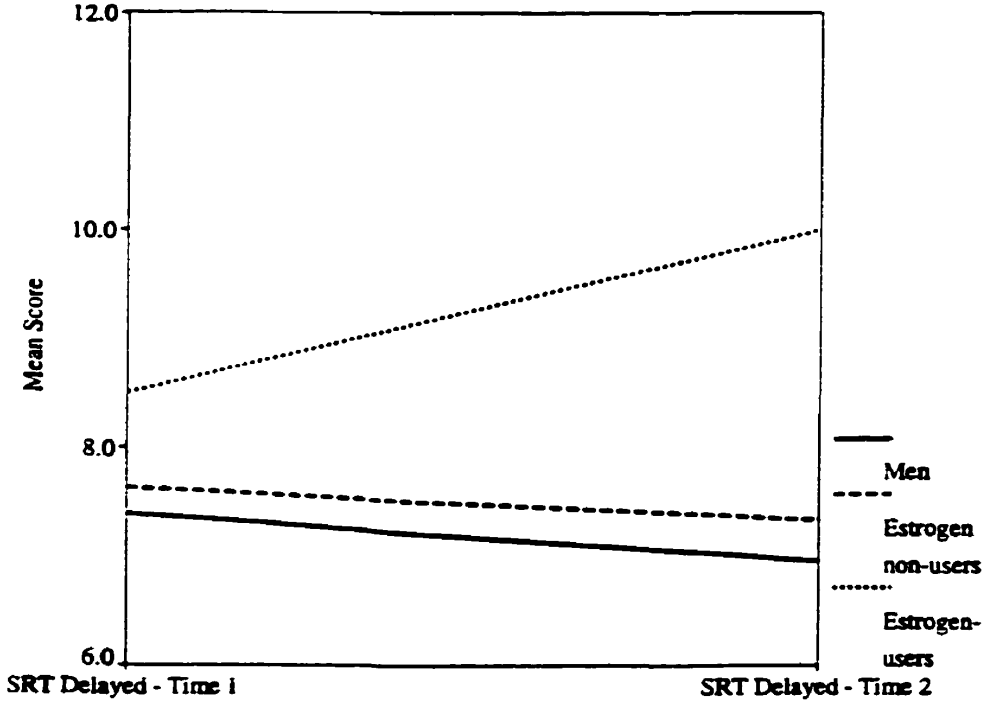
There were group but not time effects on Digit Span Total ($F[2,56]=8.08$, $p<.001$), Forward ($F[2,56]=11.98$, $p<.001$) and Backward $9F[2,56]=4.46$, $p<.02$), as reported previously at T1 and T2 independently.

Figure 1: Delayed Paragraph Recall - Times 1 and 2



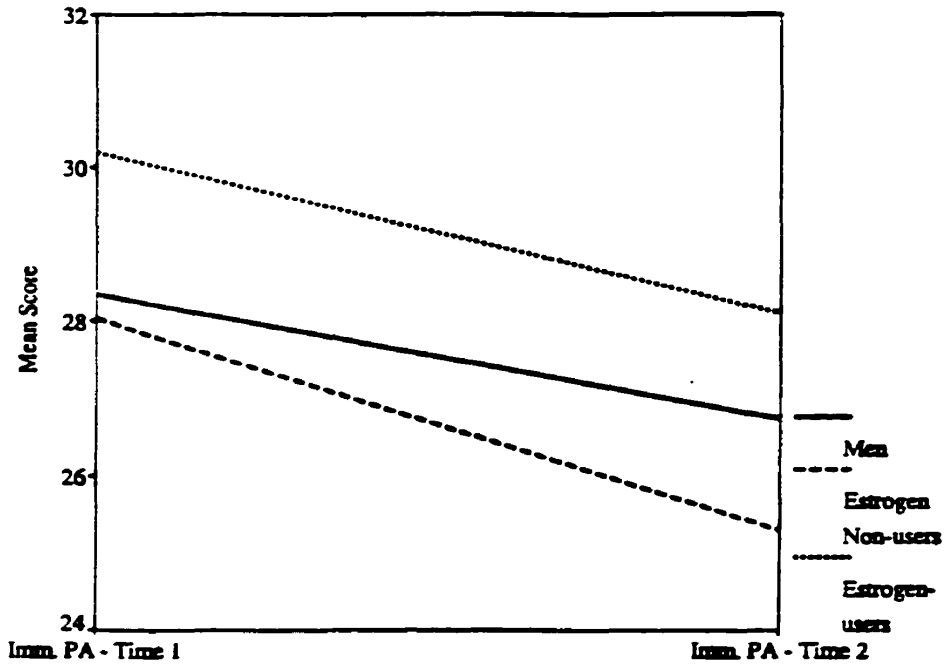
Significant interaction between group and time ($F[2,56]=5.86$, $p<.005$)

Figure 2: Delayed Selective Reminding Test - Times 1 and 2



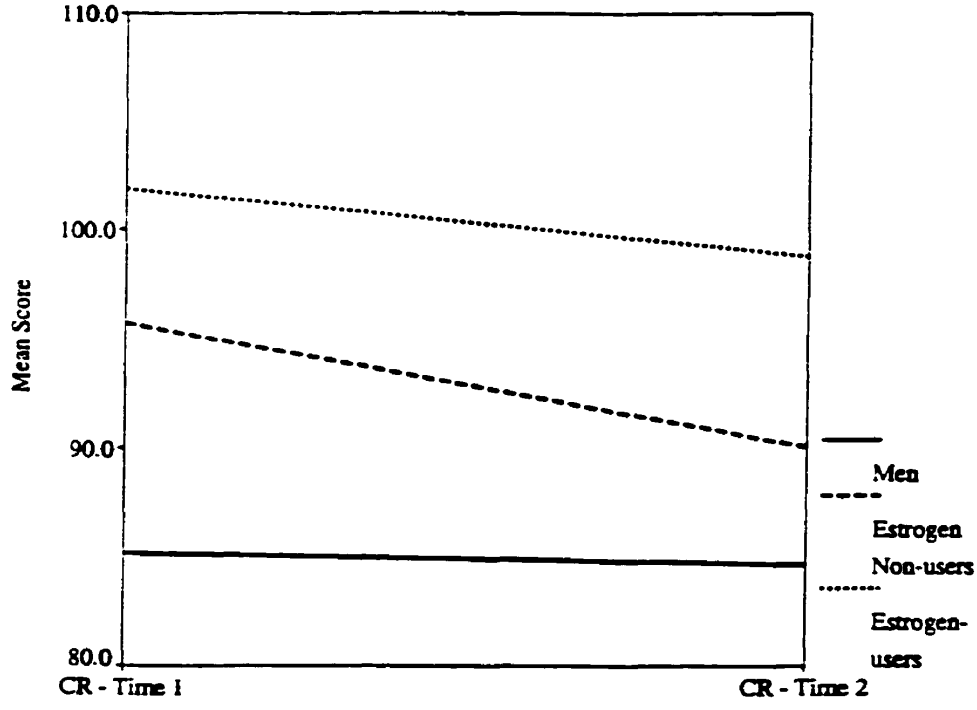
Significant interaction between group and time ($F[2,55]=3.43$, $p<.05$)

Figure 3: Immediate Paired Associates - Times 1 and 2



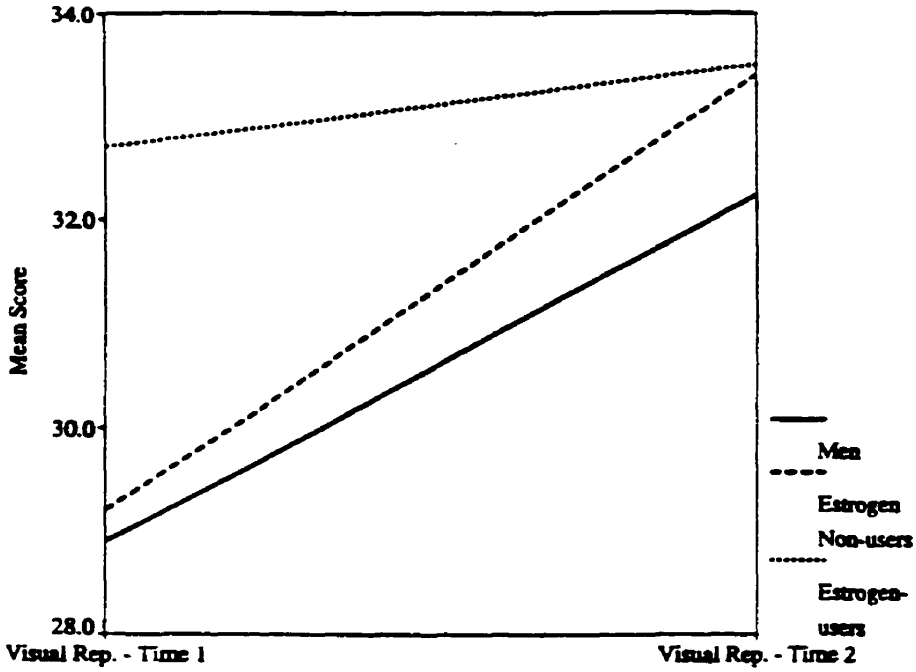
Main effect of Time ($F[1,57]=7.27$, $p<.01$)

Figure 4: Category Retrieval - Times 1 and 2



Main effect of time ($F[1,56]=4.36$, $p<.05$)

Figure 5: Visual Reproduction - Times 1 and 2



Main effect of time ($F[1,51]=10.46$, $p=.002$)

Rivermead Behavioural Memory Test Scores:

The scores of the three groups on the RBMT subtests and total score were compared using one-way ANOVA procedures with Bonferroni corrected post-hoc t-tests. The mean values are presented in Table 11. There were no significant group differences on any of the tests. The Ss scored near the maximum possible on many of the subtests, which led to low variability and probably contributed to the failure to find group differences. However, according to the RBMT manual, profile scores above 22 are considered normal, and scores between 17-21 represent "poor memory" (Wilson et al., 1985). Because the range of the Total mean scores of our Ss was 17-20, these healthy elderly individuals all had poor memory according to the RBMT norms. However, details of the normative population are not revealed in the manual. On the

Table 11
Rivermead Behavioural Memory Test Scores - Healthy Elderly

Test Name	Max. possible score	Group					
		Men		Female Estrogen Non-Users		Female Estrogen-Users	
		Mean	SD	Mean	SD	Mean	SD
Name Recall	4	2.91	1.20	3.19	1.18	3.40	0.97
Belonging	4	3.22	0.52	3.41	0.57	3.20	0.42
Appointment/Results	2	1.35	0.83	1.56	0.64	1.40	0.84
Picture Recognition	10	9.74	0.86	9.41	1.12	10.00	0
Story - Immediate	21	7.24	3.24	6.57	3.26	7.70	2.59
Story - Delayed	21	5.93	2.83	5.39	3.38	5.10	2.80
Face Recognition	5	4.57	0.66	4.85	0.36	4.80	0.42
Route - Immediate	5	4.13	0.92	4.22	0.64	4.30	1.34
Route - Delayed	5	3.91	0.95	4.30	0.61	4.40	0.70
Message	6	5.09	1.30	5.04	1.06	5.60	0.70
Orientation	9	8.87	0.34	8.78	0.42	9.00	0
Date	2	1.91	0.42	1.93	0.38	2.00	0
Total	24	17.35	3.49	17.33	3.91	19.40	2.17

other hand, scores between 16 and 24 were defined as the normal range for control Ss in a validation report of the RBMT, where the control Ss were an average age of 41 years (Wilson et al., 1989). These findings suggest that the healthy elderly Ss in this study were likely performing normally for their age.

Pearson product-moment correlations were performed between each hormone level and scores on the RBMT in each of the three groups, again using cutoff probabilities of $p<.01$. The results of these correlations are presented in Tables 12-16.

Table 12

Correlations Between Estradiol and RBMT Scores - Healthy Elderly

Test Name	Group		
	Men	Female Estrogen Non-Users	Female Estrogen-Users
Name Recall	-.061	-.093	-.136
Belonging	-.168	-.300	.407
Appointment/Results	.064	-.393	-.585
Picture Recognition	.119	-.130	na
Story Recall - Immediate	.075	-.086	.469
Story Recall - Delayed	.138	-.028	.291
Face Recognition	-.327	-.209	.490
Route - Immediate	.244	-.190	-.339
Route - Delayed	.255	-.308	-.516
Message	-.136	-.393	-.138
Orientation	-.005	.023	na
Date	-.082	na	na
Total	.064	-.406	-.196

na Correlations could not be calculated due to lack of variance

Table 13

Correlations Between Testosterone and RBMT Scores - Healthy Elderly

Test Name	Group		
	Men	Female Estrogen Non-Users	Female Estrogen-Users
Name Recall	.242	.154	.386
Belonging	-.451	.074	-.194
Appointment/Results	-.197	.022	-.212
Picture Recognition	.262	-.138	na
Story Recall - Immediate	.052	.386	-.140
Story Recall - Delayed	-.230	.382	-.554
Face Recognition	-.244	-.258	.292
Route - Immediate	.068	.363	.154
Route - Delayed	.228	.189	-.192
Message	-.185	.115	-.422
Orientation	.126	.548*	na
Date	-.122	na	na
Total	-.043	.300	-.759

na Correlations could not be calculated due to lack of variance

* P<.01

Table 14

Correlations Between Cortisol and RBMT Scores - Healthy Elderly

Test Name	Group		
	Men	Female Estrogen Non-Users	Female Estrogen-Users
Name Recall	.133	.005	.304
Belonging	-.026	.036	-.335
Appointment/Results	-.383	.113	-.941*
Picture Recognition	.417	.234	na
Story Recall - Immediate	-.056	-.366	.523
Story Recall - Delayed	-.190	-.398	.207
Face Recognition	.222	.075	.128
Route - Immediate	-.001	-.366	-.422
Route - Delayed	.082	.081	-.720
Message	.058	-.110	.235
Orientation	.235	.125	na
Date	-.092	na	na
Total	-.013	-.167	-.564

na Correlations could not be calculated due to lack of variance

* $p<.01$

Table 15

Correlations Between DHEAS and RBMT Scores - Healthy Elderly

Test Name	Group		
	Men	Female Estrogen Non-Users	Female Estrogen-Users
Name Recall	.090	-.190	.528
Belonging	.034	.057	-.705
*Appointment/Results	.082	-.218	-.301
Picture Recognition	.065	-.040	na
Story Recall - Immediate	-.003	.017	-.502
Story Recall - Delayed	-.064	-.135	-.679
Face Recognition	.147	.019	.247
Route - Immediate	.017	-.129	-.227
Route - Delayed	.123	-.149	-.118
Message	.361	-.401	.311
Orientation	-.016	.363	na
Date	-.541*	na	na
Total	.214	-.220	-.678

na Correlations could not be calculated due to lack of variance

* P<.01

Table 16

Correlations Between DHEAS/CRT and RBMT Scores - Healthy Elderly

Test Name	Group		
	Men	Female Estrogen Non-Users	Female Estrogen-Users
Name Recall	-.076	-.162	.262
Belonging	-.089	.056	-.331
Appointment/Results	.344	-.278	.329
Picture Recognition	-.189	-.182	na
Story Recall - Immediate	-.023	.237	-.824
Story Recall - Delayed	-.013	.087	-.810
Face Recognition	-.038	.032	.138
Route - Immediate	-.060	.118	.177
Route - Delayed	.005	-.104	.412
Message	.213	-.346	.139
Orientation	-.105	.368	na
Date	-.332	na	na
Total	.117	-.101	-.240

na Correlations could not be calculated due to lack of variance

Due to the invariant nature of some of the subtest scores, primarily in the estrogen-using group, correlations could not be computed for these subtests and are marked on the tables as "na". E_2 levels were not correlated with test performance in any of the groups. T levels were positively associated with performance on the Orientation test in female estrogen non-users (r=.548, p<.01) only. CRT levels were negatively correlated with the ability to remember to ask for test results in female

estrogen-users (r=-.941, p<.001), DHEAS levels were negatively associated with the men's ability to recall the proper date (r=-.541, p<.01), and the ratio of DHEAS/CRT was unassociated with any of the test scores.

To determine whether duration of estrogen treatment was related to performance on any of the RBMT subtests, years of estrogen use was correlated with test scores for the estrogen-users. No correlations were significant at p<.01.

Correlations were also performed across all Ss between the RBMT subtest scores and scores on the other neuropsychological tests to determine how performance on the everyday memory tests was related to performance on traditional neuropsychological tests. The RBMT Total Score was the most predictive of performance on traditional tests, since it was significantly positively associated with scores on seven of the traditional tests: Immediate (r=.511, p<.001) and Delayed (r=.493, p<.001) Paragraph Recall, Immediate Paired Associates (r=.492, p<.001), Immediate (r=.512, p<.001) and Delayed (r=.514, p<.001) Selective Reminding, Category Retrieval (r=.552, p<.001) and Visual Reproduction (r=.358, p<.01). Story Delayed was positively correlated with six tests: Immediate (r=.509, p<.001) and Delayed (r=.574, p<.001) Paragraph Recall, Immediate (r=.443, p<.001) and Delayed (r=.343, p<.01) Paired Associates, and Immediate (r=.506, p<.001) and Delayed (r=.424, p<.001) Selective Reminding. Story Immediate was associated with scores on five of the other tests: Immediate (r=.541, p<.001) and Delayed (r=.512, p<.001) Paragraph Recall, Immediate Paired Associates (r=.393, p<.005), Visual Reproduction (r=.402, p<.005), and Selective Reminding (r=.411, p<.001). Name Recall was

correlated with three traditional tests: Immediate (r=.382, p<.005) and Delayed (r=.346, p<.01) Selective Reminding and Category Retrieval (r=.361, p<.01). Picture Recall scores were associated with scores on Forward Digit Span (r=.342, p<.01), Route Delayed was positively correlated with Visual Reproduction (r=.362, p<.01), and Orientation scores covaried with Visual Paired Associates scores (r=.377, p<.005).

Low Vs. High Hormone Groups:

Since there were no group differences in CRT levels, a median split was conducted to create low vs. high CRT groups. The median split resulted in mixed groups of men and women in each category, based on T2 CRT levels. These two groups were compared using repeated measures ANOVA procedures to investigate the effects of CRT group on neuropsychological test performance. The mean scores used for this comparison are presented in table 17. There were no interactions between CRT group and time. Main effects of CRT group were found on Immediate Paragraph Recall (F[1,50]=4.04, p<.05), Immediate (F[1,50]=8.32, p=.006) and Delayed (F[1,50]=5.06, p=.03) Paired Associates, Delayed Selective Reminding (F[1,50]=4.99, p=.03) and Category Retrieval (F[1,50]=5.02, p=.030. In each instance, those Ss with lower CRT levels performed better than those with high CRT over both T1 and T2.

For the RBMT, administered only at T2, independent samples t-tests were performed on the mean scores of the low versus high CRT groups, which are presented in Table 18. The low CRT group scored higher than the high CRT group on the subtest of Appointment/Results (t=2.11, p<.05), in which Ss had to remember to ask the experimenter when they could hear the results of the test when prompted by a

Table 17

Neuropsychological Test Scores: Low Vs. High CRT Groups - Healthy Elderly

Test Name	T1		T2	
	Low CRT (n=26)	High CRT (n=26)	Low CRT (n=26)	High CRT (n=26)
Paragraph Recall - Immediate[a]	20.12	18.37	21.29	17.20
Paragraph Recall - Delayed	16.79	12.82	15.94	13.36
Paired Associates - Immediate[b]	30.27	26.08	28.69	23.19
Paired Associates - Delayed[c]	11.65	9.85	10.65	9.20
Selective Reminding - Immediate	53.54	50.12	52.52	49.00
Selective Reminding - Delayed[d]	8.23	7.00	8.58	6.38
Visual Paired Associates - Immediate	11.73	11.54	12.27	11.72
Visual Paired Associates - Delayed	4.81	4.62	5.12	4.56
Visual Reproduction	31.08	28.77	33.04	32.27
Figural Memory	6.65	6.96	7.19	6.92
Digit Span Total	15.92	14.73	15.50	15.52
Forward	8.81	8.31	8.96	8.52
Backward	7.12	6.42	7.08	7.12
Visual Memory Span	15.35	15.31	15.31	14.92
Forward	7.58	8.23	8.35	8.04
Backward	7.42	7.08	6.96	6.88
Category Retrieval[e]	97.69	85.35	92.92	84.27

a Low CRT > High CRT, $p<.05$

b Low CRT > High CRT, $p=.006$

c Low CRT > High CRT, $p=.03$

d Low CRT > High CRT, $p<.05$

e Low CRT > High CRT, $p<.05$

Table 18

RBMT Scores - Healthy Elderly Low Vs. High CRT Groups

Test Name	T2	
	Low CRT	High CRT
Name Recall	2.87	3.19
Belonging	3.26	3.42
Appointment/Results	1.65	1.23*
Picture Recognition	9.52	9.73
Story Recall - Immediate	7.61	6.52
Story Recall - Delayed	6.43	5.09
Face Recognition	4.70	4.73
Route - Immediate	4.13	4.15
Route - Delayed	4.04	4.15
Message	5.39	5.04
Orientation	8.74	8.88
Date	2.00	1.92
Total	18.17	17.23

* Low CRT > High CRT, $p<.05$

buzzer. This type of analysis was not done with the other hormones because there were group differences in levels of each of the other hormones which would have resulted in groups based on gender similar to those previously analyzed.

Mood Measures - Time 1:

Mood scores for each measure by group are found in Table 19.

Table 19

Mood Scores - Healthy Elderly Time 1

Test Name	Scoring Range	Men		Female Estrogen Non-Users		Female Estrogen-Users	
		Mean	SD	Mean	SD	Mean	SD
BDI	Max: 63	4.55	3.73	6.51	4.30	7.13	8.06
GDS	Max: 30	3.35	3.77	4.48	4.56	4.23	5.69
POMS 1 - elated/depressed	+18 to -18	11.81	3.94	10.80	5.53	6.21[a]	8.30
POMS 2 - clear-headed/confused	+18 to -18	14.39	3.96	13.57	4.04	12.50	5.21
POMS 3 - energetic/tired	+18 to -18	10.35	6.58	9.52	5.26	7.14	7.24
POMS 4 - composed/anxious	+18 to -18	12.61	4.24	11.38	5.73	6.29[b]	9.32
POMS 5 - confident/unsure	+18 to -18	9.71	5.19	8.05	5.32	7.00	6.59
POMS 6 - agreeable/hostile	+18 to -18	12.13	5.62	13.18	4.34	10.29	5.97
MAACL-R 1 - anxiety	Max: 10	.26	.51	.31	.73	.56	.73
MAACL-R 2 - depression	Max: 12	.52	2.01	.49	.82	.56	1.01
MAACL-R 3 - hostility	Max: 15	.55	2.16	.29	.69	.33	.71
MAACL-R 4 - positive affect	Max: 21	16.42[c]	4.30	14.18	6.10	10.67	4.58
MAACL-R 5 - sensation seeking	Max: 12	6.35	2.42	6.38	1.82	5.56	2.13

a, b Men, Female E non-users > Female E-users ($p<.01$)

c Men > Female E-users ($p<.05$)

Mood scores were analyzed with one-way ANOVA procedures followed by Bonferroni corrected post-hoc t-tests. There were no group differences on either the BDI or the GDS. According to the standard BDI norms, scores below 9 are in the normal, non-depressive range, and all three groups of our Ss fell into this range. Low scores on the GDS corroborate our Ss euthymia. The POMS contains six scales that measure different aspects of mood, and scores can range from -18 to 18 on each subscale. The POMS scales are much more sensitive to small mood fluctuations than the BDI (Lorr & McNair, 1982; McNair, Lorr & Droppleman, 1971). Female estrogen-users scored lower than the estrogen non-users and the men on the POMS 1, which measures depression-elation ($F[2,82]=5.18$, $p<.01$), and the POMS 4, the anxious-composed scale ($F[2,82]=4.08$, $p<.02$), indicating that they felt less elated and less composed than the other groups. However, mean scores of all three groups fell within the range of normal values. The estrogen-using women also scored lower than the men on the MAACL-R 4, which measures positive affect ($F[2,82]=3.98$, $p<.05$), consistent with the results of the POMS 1 scale.

Pearson product-moment correlations between E_2 and mood scores were calculated for each group (Table 20). No correlations were significant at the $p<.01$ level. To investigate whether the effects of a combined estrogen-progesterone treatment affected mood differentially, the same analyses were done excluding the three estrogen-using women who were also taking progestins. After exclusion of these three women, the mood scores between the estrogen-users and non-users were no longer statistically different. The mean scores of the estrogen-using women changed

Table 20

Correlations between Estradiol and Mood Scores - Healthy Elderly Time 1

	Men	Female Estrogen Non-Users	Female Estrogen-Users
BDI	.162	.341	-.122
GDS	.115	.186	-.120
POMS 1 - elated/depressed	.061	-.145	-.185
POMS 2 - clear-headed/confused	.043	-.076	.008
POMS 3 - energetic/tired	-.263	-.155	-.051
POMS 4 - composed/anxious	-.339	-.190	.035
POMS 5 - confident/unsure	-.007	-.069	-.199
POMS 6 - agreeable/hostile	-.192	-.346	.173
MAACL-R 1 - anxiety	-.083	.163	-.145
MAACL-R 2 - depression	-.040	.263	-.338
MAACL-R 3 - hostility	-.084	-.122	-.547
MAACL-R 4 - positive affect	.097	-.254	-.305
MAACL-R 5 - sensation seeking	-.062	-.232	-.538

no significant correlations

from 6.21 to 8.64 on the POMS 1, from 6.26 to 8.82 on the POMS 4, and from 10.67 to 11.71 on the MAACL-R 4 with the removal of the three women taking combined estrogen and progestin therapy. The cognitive findings remained unchanged.

Mood Measures - Time 2:

At T2, the POMS and the GDS were re-administered. The mean scores on these measures and the correlations between each measure and T2 E_2 levels for each group are presented in Table 21.

Table 21
Mood Scores and Correlations Between Mood and Estradiol Levels - Healthy Elderly Time 2

Group		POMS 1	POMS 2	POMS 3	POMS 4	POMS 5	POMS 6	GDS
	Possible Range	-18 to +18	-18 to +18	-18 to +18	-18 to +18	-18 to +18	-18 to +18	Max. 30
Men (n=23)	Mean	11.69	14.04	9.96	12.70	10.26	13.70	3.52
	SD	4.59	4.50	5.81	5.00	5.94	4.06	3.52
	Correlation with E_2	-.234	.081	-.338	-.089	-.162	-.324	.020
Female Estrogen non-users (n=26)	Mean	10.15	12.77	9.15	11.27	7.65	11.96	5.00
	SD	6.00	5.54	5.40	4.62	6.45	4.40	4.92
	Correlation with E_2	-.231	.221	.176	.089	.254	.036	.128
Female Estrogen-users (n=10)	Mean	8.10	12.30	8.70	9.20	9.60	11.5	3.27
	SD	6.01	3.02	4.53	6.81	4.84	3.84	3.93
	Correlation with E_2	.391	.172	.114	.485	.304	.260	-.498

There were no significant group differences on any of the mood measures, nor were any correlations found between E_2 levels and mood measures.

Discussion

Hormone Levels

Results of the radioimmunoassays of the four steroid hormone levels that were measured showed that both the men and the estrogen-using women had higher levels

of plasma E_2 than the estrogen non-users, at both test times. However, whereas the estrogen-users had E_2 levels within the range of menstrual cycle values, E_2 levels of both the female non-users and the men fell within the range of postmenopausal values (<100 pmol/L), which coincides with the lower third of the normal male range of E_2 levels (37-220 pmol/L). Although it may seem counterintuitive that 72 year old men had higher E_2 levels than untreated age-matched women, it is important to recall that the ovary is the major source of estrogen in women and that the ovarian production of both E_2 and E_1 decreases to negligible levels within 24 months of the last menses (Longcope, 1986). In men, however, 80% of plasma E_2 arises from the peripheral conversion of T (Braunstein, 1986). Although T levels decrease with increasing age in men (Tenover, 1996), production never ceases entirely so that the prohormone for the metabolism of E_2 is available to men lifelong. Therefore, despite the slight, yet significant decrease in E_2 levels with increasing age in healthy males (Simon et al., 1992), which was confirmed in our sample, elderly men still had higher plasma levels of E_2 than untreated elderly women.

The procedure for this study required that the women be tested prior to the blood sampling and the men be tested after the sampling, due to the restricted availability of the nurse who took the samples. Thus, all samples were collected at the same time of day to control for any differences in hormone levels due to diurnal variation. Two possible confounds arise from this methodology. First, it is known that CRT is responsive to stressful stimuli, and can be elevated after stressful mental tasks (Bohnen, Houx, Nicolson & Jolles, 1990; Kirschbaum, Wolf, May, Wippich &

Hellhammer, 1996). Thus, elevated CRT levels may have been evident in the women because the blood sample was drawn after the conclusion of the test session, which may have been perceived as stressful. However, it is also possible that the men may have been anticipating stressful mental activity when their blood sample was drawn, which might have led to elevated CRT levels as well. Despite these possibilities, no gender differences occurred in CRT levels, and all three groups had levels well within the normal range of CRT levels (Table 4). This argues against the possibility that the tasks posed a significant stress. As well, CRT levels were not different at T2 compared to T1, except in the estrogen non-users where they increased. The second test session should have been less stressful, since at that time the Ss were familiar with the tasks. However, the stability in CRT levels over a year and a half in two of these groups does not reflect this possible change in stress levels. The increase in CRT levels only in the women estrogen non-users but not the estrogen-users, who were exposed to the same procedure, also argues against a stress-related elevation in CRT. Thus, it does not appear that the test battery was stressful enough to have significantly elevated CRT levels in these Ss, and therefore it is unlikely that the timing of the blood sample was a significant confound.

The second issue arising from this methodology relates to the timing of the test battery, and will be discussed under neuropsychological test results.

The changes in hormone levels observed over one and a half years confirmed our expectations, with a few exceptions. There was no reason to believe that CRT levels would change over time in any group (Sharma et al., 1989; Sherman et al.,

1985; Waltman et al., 1991), and no changes in the levels of E_2 or T were expected in the estrogen-using women since the doses in their hormone regimen had remained stable. E_2 and T were expected to remain stable in the estrogen non-users as well, having already declined shortly after the menopause to low and relatively stable levels (Longcope, 1994). However, it was predicted that E_2, T and DHEAS would decline in the men (Tenover, 1996; Vermeulin, 1995) and DHEAS would decline in both groups of women (Hornsby, 1995; Vermeulin, 1995) due to the effects of aging. ERT should not have differentially affected levels of DHEAS, since the decline in estrogens at the menopause is not considered to be causally related to the age-associated decline in DHEAS levels (Longcope, 1994). Therefore, estrogen replacement after the menopause would not be predicted to influence DHEAS levels.

Indeed, little change occurred in E_2 levels in both groups of women after a year and a half, whereas E_2 levels in the men decreased over time, as predicted. T levels remained stable in all three groups from T1 to T2, contrary only to the hypothesis that they would decline in men. The failure to find a decrease in T levels in men could have been due to the relatively short interval between test times. Most aging studies have been cross-sectional and have reported differences in T levels only when comparing individuals in different decades of life (Pike & Doerr, 1973; Dai et al., 1981; Davidson et al., 1985; Simon et al, 1992), whereas others have failed to find age-related declines in T levels in men (Harman & Tsitouras, 1980; Naeves, Johnson, Porter, Parker, & Petty, 1984; Sparrow, Bosse & Rowe, 1980). Depressed T levels have been reported in men with ill health (Tenover, 1996). However, the men in our

sample were in good health at both testing times. Thus, considering the good health of these men and the relatively short time period of the follow-up, the observation of no decreases in T levels is not unprecedented.

The finding that DHEAS levels did not decline in any of the groups is inconsistent with Vermeulen's (1995) observation from cross-sectional data of a 2% decrease in DHEAS levels per year until at least age 80, and with results from a one-year longitudinal study that recorded an 11% decline in DHEAS levels in men (Thomas et al., 1994). Since the 72 year-old men in our sample had DHEAS levels below the lower limit of the normal male range, it is perhaps unlikely that levels would have decreased further over the next one and a half years. The DHEAS levels in the women were also extremely low at T1.

CRT levels increased in only the estrogen non-using women over the year and a half between test sessions. This was inconsistent with other studies that have shown stability of CRT with aging (Sharma et al., 1989; Sherman et al., 1985; Waltman et al., 1991). However, one study identified a subgroup of elderly individuals whose CRT levels increased over time (Lupien et al., 1995). Thus, the estrogen non-using group in our study may have consisted of more individuals with this pattern of increasing CRT secretion than the men and estrogen-users.

Neuropsychological Tests

The major neuropsychological findings of this investigation of three groups of 72 year-old Ss were that, at T1, the men and the women estrogen-users performed significantly better than the age-matched women estrogen non-users on Total and

Forward Digit Span. Moreover, the estrogen-using women scored better than the non-users on Backward Digit Span as well. Additionally, both groups of women had higher scores than the men on the Category Retrieval test, which measures language fluency, or nondeclarative verbal semantic memory (Tulving, 1983). The finding that the women outperformed the men on the language fluency test is consistent with sex differences in this ability reported in the past (Hampson & Kimura, 1992; Hyde & Linn, 1988; Jarvik, 1975). Results similar to those from T1 were found on the Digit Span test at T2, in that the estrogen-users and the men outperformed the estrogen non-users on Forward Digit Span, and the men scored higher than the estrogen non-users on Total Digit Span. The estrogen-using women also improved on the Delayed Selective Reminding test over time compared to the men and the estrogen non-users, but decreased on Delayed Paragraph Recall compared to the men. As well, at T2 Ss with lower CRT levels performed better on several explicit verbal memory tests than those with higher CRT.

It has been suggested that the administration of estrogen to healthy postmenopausal women improves performance on measures of newly learned verbal information, or explicit memory (Sherwin, 1997), which is dependent on the hippocampal memory system (Squire, 1992). In some reports, female estrogen-users performed better on Digit Span than non-users (Sherwin, 1988a), but this difference has not been found consistently (Ditkoff et al., 1991). Although, in this study, female estrogen-users performed better than non-users on Forward, Backward and Total Digit Span, the neural basis of this finding is unclear. Digit Span, in general, has been

characterized as a measure of attention and concentration (Lezak, 1995), and of short-term memory (Craik, 1994; Kolb & Wishaw, 1995). Several authors have argued that Forward and Backward Digit Span are conceptually distinct tasks, involving not only different cognitive skills, but different brain areas as well (Banken, 1985; Griffin & Heffernan, 1983). Forward Digit Span, which requires attention as well as short-term memory, does not appear to be as heavily dependent upon the medial temporal lobe hippocampal memory system as other verbal memory tasks, since lesions to this area do not cause severe deficits on this task (Kolb & Wishaw, 1985, p. 495; Moscovitch & Winocur, 1992). In fact, lesions to the left parietal lobe (Warrington & Weiskrantz, 1973; Kolb & Wishaw, 1990) can cause impairments in short-term memory, particularly on Forward Digit Span. Additionally, some attentional processes are dependent upon the anterior dorsolateral frontal cortex (Lezak, 1995) and attention has also been linked to the neurotransmitter norepinepherine (McEntee & Crook, 1990).

Backward Digit Span, which requires working memory as well as short-term memory and attention, appears to involve more hippocampal regions, since amnesic patients with hippocampal lesions show impaired performance on tasks which have a working memory component (Moscovitch & Winocur, 1992). Thus, our findings of superior Forward Digit Span performance in estrogen-using women and men compared to estrogen non-using women may represent estrogenic actions in areas of the brain other than the hippocampus, perhaps the frontal or parietal lobes, or may involve the neurotransmitter norepinepherine. Indeed, while estrogen influences morphology and neurotransmitter levels in the hippocampus and adjacent cortex in rats

(McEwen, et al., 1995), it may also act on ERs in other areas of the cortex (Simerly et al., 1990). Additionally, there are instances in which E_2 influences the neurotransmitters dopamine and norepinepherine throughout the brain in the absence of detectable ERs (McEwen et al, 1996; DiPaulo, 1994). This raises the possibility that E_2 may be acting on brain areas and neurotransmitter systems that support both Forward and Backward Digit Span as well as other explicit verbal memory functions.

It is also noteworthy that the brain contains the aromatizing enzyme necessary for the conversion of T to E_2 (Naftolin & Ryan, 1975). The fact that male testes continue to secrete T lifelong, together with the ability of the brain to convert T to E_2 suggests that E_2 is available to male brains throughout their lifespan while it is unavailable to the brains of untreated postmenopausal women. This speculation gains support from the finding of higher E_2 levels in our healthy elderly men than in our age-matched estrogen non-users. If it is the case that E_2 enhances cognitive function in elderly men as well as in postmenopausal women, then this might explain why the elderly men outperformed the age-matched female estrogen non-users on Forward and Total Digit Span in the present study.

Despite the superior performance of estrogen-users on Forward, Backward and Total Digit Span, they did not perform significantly better than the non-users, or the men, on tests of explicit verbal memory, with the exception of the Delayed Selective Reminding test at T2. Two other tests in our battery, Paragraph Recall and Paired Associates, also measured explicit verbal memory. Although scores did not differ significantly between the three groups on Paragraph Recall or Paired Associates, it was

clear that, in absolute terms, the women receiving estrogen had higher scores than both of the other groups on these tests, and on all other neuropsychological tests administered except for Figural Memory and Visual Memory Span, in which the men excelled (Table 5). There is a possibility that between group differences on these tests of explicit verbal memory were not significant due to the small sample size of the estrogen-user group (n=14). Indeed, this possibility is supported by the findings of previous studies in which E_2 enhanced verbal memory (Hackman & Galbraith, 1976; Kampen & Sherwin, 1994; Phillips & Sherwin, 1992; Sherwin, 1988). Moreover, the improved performance of the estrogen-users at T2 on the Delayed Selective Reminding test relative to the men and estrogen non-users supports a possible maintenance effect of E_2 on verbal memory. Why this effect did not occur on the other tests of verbal memory is unclear, but may have to do with the different nature of the tasks. The Selective Reminding Test measures a type of rote memory the requires mental rehearsal, while Paragraph Recall assesses logical memory of ideas presented in a story format. The possible differential effect of estrogen administration on specific verbal memory tests requires further investigation.

There were no correlations between E_2 levels and neuropsychological test scores in any of the groups at either test time. Due to the exploratory nature of the study, a large number of correlations were conducted. Thus, we used a conservative significance level of $p<.01$. With low and relatively invariant levels of hormones as were found in these elderly men and women, and considering the small sample of estrogen-using women, it is not surprising that no significant correlations were found.

This failure to find correlations between E_2 and memory scores is consistent with Kampen & Sherwin (1994), in which plasma E_2 levels were uncorrelated with scores on similar neuropsychological tests in elderly female estrogen-users and non-users. It is, however, inconsistent with a study of surgically menopausal women receiving estrogen replacement therapy (Phillips & Sherwin, 1992a) in which E_2 levels were positively associated with Immediate Paired Associates scores. In the latter study, plasma E_2 levels were supraphysiologic at the time of testing, which may have accounted for the significant correlation. In our women whose E_2 levels were either in the low range of physiological values for naturally cycling women, or in the postmenopausal range, no such correlations were apparent. Kampen & Sherwin (1996) found a positive correlation between E_2 and visuospatial skills on the Mental Rotations test in men. In the present study, no correlations between E_2 and any of our visual memory tasks occurred in the men; however, we did not directly assess spatial skills. Thus, our finding of no correlations between E_2 and test scores in any of the three groups corroborate the existing literature.

With respect to changes in neuropsychological test scores, performance decreased in all subjects over the year and a half between test times on Immediate Paired Associates and Category Retrieval. Age-associated decreases in scores of explicit verbal memory are common, particularly on tasks such as Paired Associates (Craik, 1994). In these instances, estrogen-use did not protect against the age-associated decrements in performance. Despite the decreases, however, absolute scores on these two tests were higher in the estrogen-users than the non-users and the men

at both test times. There was also a time-related improvement on the Visual Reproduction test across groups. Although a hormonal explanation for this finding is not apparent, it could have been due to practice effects, since at T2 the same drawings were used as at T1 due to the lack of a parallel form for this subtest.

When compared to the men, the estrogen-users scores on Delayed Paragraph Recall decreased over one and a half years (Figure 1), which was unexpected. Examination of the individual data of the estrogen-users showed that in two of the ten Ss. scores on Delayed Paragraph Recall had decreased substantially from T1 to T2 (14 and 16 point decreases), while scores of the other eight estrogen-users had remained relatively stable across time. Therefore, the data of only two women accounted for the interaction between group and time that was observed. One of these women scored only 3.5 on the Delayed Paragraph Recall at T2. She complained at the beginning of the test session that she was very nervous, and continued to express anxiety throughout the session. Anxiety could have accounted for her poor performance by interfering with initial encoding and later retrieval of the stories. This same S was also one of the three estrogen-users who was taking combined estrogen-progestin therapy. Since progesterone can oppose the actions of E_2 in the hippocampus (Murphy & Segal, 1996), combined therapy may have hampered her performance on this hippocampally-dependent task.

The other woman whose score decreased over time was the highest scorer on Delayed Paragraph Recall at T1. Although her score at T2 on this test was very near the average, the difference between her superior performance at T1 and her average

performance at T2 was quite drastic. When the data for these two Ss are eliminated, there were no group differences on the Delayed Paragraph Recall Test between test times. The absence of an estrogenic effect on tests of visual memory is consistent with earlier studies (Kampen & Sherwin, 1994; Phillips & Sherwin, 1992) and supports the notion that estrogen does not enhance visual/spatial memory (Phillips & Sherwin, 1992).

Because T levels were higher in men than in both female groups, it might have been expected that the men would outperform both female groups on tests measuring visuospatial skills (Hampson & Kimura, 1992). However, this did not occur in the present study possibly because the tests we used did not properly assess the domain of spatial skills that T is purported to influence (Gordon & Lee, 1986; Errico, Parsons, Kling & Kling, 1992; Janowsky, Oviatt, & Orwoll, 1994), since the focus was on visuospatial *memory*. For example, a test of Mental Rotations, as opposed to Figural Memory or Visual Reproduction, might have demonstrated a male superiority as it did in these other studies. As well, the 72 year-old men in this study had T values in the lower third of the normal male range, which may have precluded any effects of these sub-threshold values. The finding that T levels were not related to the visuospatial memory tasks that were administered suggests that while T may influence visuospatial *skills*, it does not play a role in the more complex processes involved in visuospatial memory.

In the estrogen-using women, an interesting pattern of positive correlations occurred at T1 between most test scores and T levels (Table 7). Significant positive

correlations occurred between T , Delayed Paragraph Recall and Category Retrieval, both tests of verbal memory, and RBMT Orientation (Table 14), which were not predicted. However, no such correlations were found in the estrogen non-using women, who had somewhat higher T levels and a greater range of scores. Others have reported that women with higher T levels outperformed those with lower levels on spatial tasks (Gouchie & Kimura, 1991), but there were no correlations in that study between T levels and cognition in women. In our subjects, although the values of the estrogen-users appeared to be lower than those of the non-users, there was no statistically significant difference in T levels between the female groups. However, within the estrogen-users group, higher T was related to better performance. It has been suggested that the effects of T on cognition may follow a curvilinear function such that there exists a certain optimal level for peak performance above which elevated levels are detrimental (Gouchie & Kimura, 1991; Shute, Pellegrino, Hubert & Reynolds, 1983). Perhaps the estrogen-using women in this study had such low T levels that they represent the increasing arc of such a function, so that within this group higher T levels were associated with better test performance.

The positive relationships between T values and visuospatial orientation in men that have been reported previously occurred in young men who also had considerably higher T values than those of the elderly participants in this study (Errico et al., 1992; Gordon & Lee, 1986). Indeed, in another study of elderly men, no correlations between T levels and visuospatial test scores were found (Janowsky et al, 1994). While this suggests that the low and restricted range of T levels in elderly men

precludes correlations with visuospatial test scores, a recent study of young men also failed to document this hormone-behaviour relationship (Kampen & Sherwin, 1996). The reason for the inconsistency in these findings in young men is unclear at the present time, but for older men with low T levels, such hormone-behaviour correlations have not occurred in any study in which they were investigated.

The increase in CRT levels across one and a half years in the estrogen non-using women was unpredicted but not without precedent (Lupien et al, 1994). In one study, women whose CRT levels increased over time and who had relatively high CRT levels at the time of testing were cognitively impaired compared to control subjects (Lupien et al, 1994). Some evidence from our study corroborates that finding. For example, based on a median split, Ss with high CRT levels at T2 were impaired compared to Ss with low CRT levels on Immediate Paragraph Recall, Immediate and Delayed Paired Associates, and Delayed Selective Reminding, all tests of explicit verbal memory. As well, at T2 negative correlations occurred between Remembering an Appointment and CRT levels in estrogen-users and between both Immediate Paired Associates and Delayed Selective Reminding and CRT levels in estrogen non-users. This finding of negative correlations between CRT levels and explicit verbal memory only in women may reflect the greater sensitivity of the female hippocampus to glucocorticoids, as suggested by the greater number of GRs in female compared to male rat hippocampi (Turner & Weaver, 1985). If the same holds true for humans, this sex difference may be exacerbated after the menopause, since OVX led to increased concentrations of GRs in the female hippocampus, but castration did not

affect GRs in males (Turner & Weaver, 1985).

Explicit memory performance, measured by the aforementioned tests, is dependent upon the hippocampus (Squire, 1992). Elevated CRT levels resulted in cell death in the CA1 and CA3 layers of the hippocampus in rats (Wooley et al., 1990), monkeys (Uno et al., 1994) and humans (Starkman et al., 1992). These studies suggest the possibility that higher CRT levels may be causing cell death in the hippocampus of these elderly men and particularly in the women, which would explain our findings of worse explicit memory performance in those Ss with higher CRT. These results, along with those of Lupien et al (1994), are the first to demonstrate detrimental effects of CRT in healthy elderly men and women who have CRT levels within the normal range.

CRT levels were positively associated with Total Digit Span scores in the men, but were negatively associated with test performance in the women, as discussed above. That higher CRT levels were associated in the men only with Digit Span performance may be an indication that, in this instance, higher CRT levels caused an arousing / motivating influence and improved attention. Indeed, higher doses of CRT facilitated avoidance learning in rodents and performance on attentional tasks in men (Beckwith et al., 1986; deWeid, VanWimersma Griedanus & Bohus, 1974). Why higher CRT would exert both an arousing effect on short-term memory / attention and a detrimental effect on longer-term explicit verbal memory is cause for speculation, but such paradoxical effects have been described in the literature and may have to do with the two types of glucocorticoid receptors and the different functions they subserve

(McEwen et al., 1993), as well as the different brain areas associated with these two types of tasks (Kolb & Wishaw, 1990; Lezak, 1995).

DHEAS levels (Table 9) and the DHEAS/CRT ratio (Table 10) correlated positively with some of the neuropsychological tests in the men (Immediate Selective Reminding Test, Forward and Total Digit Span), but correlated negatively with the same test scores in the estrogen non-using women. If DHEAS was protective against cognitive decline as others have suggested (Svec & Lopez-S, 1989), positive correlations between DHEAS levels and cognitive performance would be expected. It could be that such positive associations exist only for males, as much of the previous research has focussed on male rodents (e.g. Flood et al, 1998, 1992). It is also possible that DHEAS effects are not likely to be seen in a population with such low and invariant levels as those observed in these individuals. In a large epidemiologic study, DHEAS levels were positively correlated only with the Selective Reminding Test and only in women, and the finding was dismissed as a spurious result of multiple comparisons (Barrett-Connor & Edelstein, 1994). Some investigators have found that AD patients had lower DHEAS levels than control Ss (Sunderland et al., 1989; Nasman et al, 1991; Yanase et al., 1996), but no correlations between DHEAS levels and test performance in either AD patients or controls occurred even in those samples. The ratio of DHEAS/CRT in this study was inconsistently related to memory performance in both men and women. Therefore, although the DHEAS/CRT ratio measure may have some validity in pathological populations such as AD patients (Leblhuber et al, 1993; Svec & Lopez-S, 1989), it may not be relevant in healthy

populations with normal levels of CRT and DHEAS.

As mentioned previously, the cognitive testing was conducted between 10 AM and noon in the women, and between noon and 2 PM in the men. Generally, people are more alert in the morning and show a post-lunch dip in cognitive performance, particularly in attention (Monk, Buysse, Reynolds, Kupfer, 1996; Monk, Buysse, Reynolds, Kupfer, Houck, 1996). If this performance dip occurred in our elderly Ss, we would have expected that the men, who were tested after lunch, would have performed worse than both groups of women, who were tested just before lunch. However, this only occurred in the case of the Category Retrieval test, in which women generally outperform men regardless of the time of day (Jarvik, 1975). On other tasks, such as Digit Span, which measures attention and short-term memory, the men performed better than the estrogen non-users and similarly to the estrogen-users, though both of these groups were tested in the morning. Thus, the pattern of results does not provide any reason to believe that a post-lunch dip in performance or attention occurred in the men, particularly since the men unexpectedly outperformed the women estrogen non-users on the attentional task of Digit Span. Indeed, in more elderly Ss, alertness rhythms did not conform to the usual pattern of the post-lunch dip (Monk et al., 1996), so it is possible that this may be the case in our 72 year-old men and women.

RBMT Subtests

The absence of group differences on the RBMT subtests may reflect a ceiling effect on this test in these healthy 72 year olds. Although scores were generally high,

only the estrogen-using women scored perfectly on any of the subtests. In fact, every estrogen-user had the highest possible score on Picture Recognition, Orientation and Date, and the overall Total Score for the estrogen-users of 19.4 was slightly (although not significantly) higher than the other two groups, both of whom scored a mean of 17.3.

Correlational analyses of the RBMT subtests and the traditional neuropsychological tests provided some information regarding which neuropsychological functions these face-valid everyday memory tasks may be measuring. Explicit verbal memory test scores from the traditional test battery were related to performance on the RBMT Total Score and to performance on RBMT Immediate and Delayed Story Recall. The high positive correlations between Paragraph Recall and Story Recall were expected, since they test the same function in a similar format. The positive correlations between the RBMT Total score and such a high number of explicit verbal memory tasks suggests that overall the RBMT is measuring explicit verbal memory rather than visual or spatial memory. These associations also suggest that many aspects of everyday memory are based on explicit verbal memory skills. Name Recall performance on the RBMT was also positively associated with explicit verbal memory, which suggests that remembering a name may be similar to remembering other verbal information. Picture Recognition scores were related to performance on Forward Digit Span, which could mean this task may require short-term memory and concentration. Route Recall and Visual Reproduction performance were positively associated, which supports the idea that the route finding

task is a measure of visuospatial function.

The finding that overall, the RBMT seems to be measuring skills related to those that have been reported as enhanced by estrogen-use (explicit verbal memory), suggests that the type of everyday memory measured by the RBMT may also be sensitive to estrogen-use. If this is the case, then estrogen-users may find some benefits of estrogen-use in their everyday lives as well as on standard laboratory tests of cognition. The estrogen-users in this study did not perform significantly better than the other groups on the RBMT, but this could have been due to a ceiling effect, as previously discussed. More difficult everyday memory tasks may be more sensitive to performance differences between estrogen-users and non-users.

Mood Measures

Although the estrogen-using women showed less elation and positive affect and felt less composed than the men and the estrogen non-users at T1, when the three women who were also taking a progestin were excluded from the analyses, there were no longer any differences in mood between the estrogen-users and the non-users. This highlights the mood-dampening effect of progestins co-administered with estrogen replacement therapy, and is consistent with a number of clinical studies of combined estrogen and progestin administration which found a decrease in mood compared to the administration of estrogen alone (Sherwin, 1991; Magos et al., 1986; Holst, Backstrom, Hammerback, & VonSchoultz, 1989). Interestingly, a reanalysis of the cognitive test results excluding the scores of the three women taking combined estrogen-progestin therapy found no differences compared to analysis of the full

sample. This suggests that while the addition of a progestin to an estrogen replacement regimen dampened mood, it did not significantly influence cognitive performance in this sample of women.

On average, the Ss in this study scored above the normative samples for positive mood on the MAACL-R and POMS. All three groups had lower than average anxiety and hostility and higher sensation seeking for their age group on the MAACL-R (Zuckerman & Lubin, 1985). Their high level of sensation seeking may have prompted them to answer our advertisement in the newspaper and voluntarily subject themselves to an unfamiliar and possibly anxiety-provoking testing situation. Even though the estrogen-users scored lower than the other two groups on the MAACL-R positive affect scale, their scores did not differ with respect to the normative sample, whereas scores of positive affect in the men and estrogen non-using women were higher than the normative average score. On the GDS and BDI all three groups scored well within the normal range. The consistency of these findings derived from four mood measures suggests that these volunteer Ss were self-selected for higher than normative positive affect. Although the incidence of clinical depression in the elderly is not higher than in individuals between the ages of 25-44 years (Myers et al., 1994), the prevalence of significant depressive symptoms that do not meet formal diagnostic criteria has been reported at 20% among community-dwelling elderly men and women (Scogin, 1994). The lack of such depressive symptomatology in our Ss confirms this self-selection bias with respect to normal mood.

Sample Characteristics

Several characteristics of our sample merit attention. Compared to the normative sample used in the standardization of the WMS-R (Wechsler, 1987), our Ss obtained higher mean scores on the majority of the tests. The standardization sample for this battery of memory tests was based on U.S. census data (1980) in which over 50% of the 70-74 year old subjects had 0-11 years of education, 20% had 12 years of education, and only 20% had any post-secondary education (Wechsler, 1987). In contrast, our sample was of higher educational status, with an average of over 12 years of education. All three groups outperformed the WMS-R standardization sample on all but the tests of Immediate and Delayed Paragraph Recall.

The female estrogen-users in our sample were of a higher socio-economic status and had more years of education than the estrogen non-using women at T1, a finding that has been discussed previously in the literature as a confound in naturalistic research. For this reason we covaried out the effects of SES and education on all the neuropsychological tests, which resulted in decreases to the absolute scores on the tests of Immediate and Delayed Paragraph Recall, Immediate and Delayed Paired Associates, and Immediate Visual Paired Associates. This indicates that educational status is most highly correlated to performance on those tests that measure explicit verbal memory, precisely those in which estrogen-users tend to excel. The observation that elderly women who are estrogen-users are of a higher SES than non-users is common in this literature and may reflect their preferential access to medical services, greater awareness of preventive health techniques and greater financial resources with which to seek optional medical treatments. This confound between estrogen-use,

education, and SES in elderly women can only be overcome by prospective, controlled studies of homogeneous groups of women. That these demographic differences were not found at T2 seemed to have been due to the smaller sample sizes, since the absolute values of SES and education did not change significantly (Table 1).

It is unlikely that the inclusion of both surgically and naturally menopausal estrogen-users in this study confounded the results. Although levels of E_2 and E_1 are higher in naturally postmenopausal women compared to surgically menopausal women for two years after the cessation of menses, progressive ovarian atrophy occurs over time so that differences in E_2 levels between surgically and naturally menopausal women are no longer apparent two years after a natural menopause (Longcope, 1986). Therefore, from the perspective of reproductive endocrinology, the distinction between naturally and surgically postmenopausal 72 year-old women with an average time of 22 years since the menopause is unimportant.

Summary

Both groups of women performed better on tests of verbal fluency than the men, consistent with known sex differences in this ability, and the men and female estrogen-users performed better than the estrogen non-users on Total and Forward Digit Span at both test times. Female estrogen-users also performed better than non-users on Backward Digit Span and better than both the men and non-users on the Delayed Selective Reminding test. To the extent that estrogen increases the synthesis of acetylcholine (Luine, 1985), increases the density of dendritic spines in the CA1 layer of the hippocampus (Wooley et al., 1992), and decreases the rate of degradation

of norepinepherine (Luine et al., 1975) in brains of both sexes, the increased availability of estrogen to the aging brain would serve to maintain memory functions in both men and women. The direct evidence from the present study in support of this hypothesis is the finding that estrogen-users and men performed significantly better than estrogen non-users on Total and Forward Digit Span, a verbal test of attention and short-term memory, and that the estrogen-using women performed better than the other groups on Delayed Selective Reminding.

Those elderly men and women with higher CRT levels showed worse memory performance on explicit verbal memory tests compared to those with lower CRT, which is consistent with the detrimental effects of elevated CRT in the hippocampus (Wooley et al., 1990; Uno et al., 1989; 1990; 1994; Sapolsky et al., 1990), and with clinical studies which have found elevated CRT to be associated with poorer memory performance (Starkman et al., 1992, Wolkowitz et al., 1990; Lupien et al., 1994). Therefore, these findings in healthy elderly men and women further support the notion that higher CRT levels may be associated with poorer memory performance in aging individuals.

Overall, the estrogen-users in this study were less elated and composed than the women estrogen non-users and men, and showed less positive affect than the men. However, when the three estrogen-users who were also taking progestins were removed from the analysis, the mood scores between the three groups were not different. This finding emphasizes the possibly mood-dampening effects of adding a progestin to estrogen replacement therapy and raises questions about the consequences of combined

therapy for the majority of women who are compelled to take progestins to protect the uterus from endometrial hyperplasia that may result from treatment with E_2 alone.

Study 2 - Steroid Hormone Levels and Everyday Memory in AD patients

Introduction

Considering that women who took estrogen were less likely to develop AD (Tang et al., 1996; Paginini-Hill & Henderson, 1994), and that estrogen administration enhanced memory in women with AD in several small uncontrolled trials, this study was undertaken to investigate the relationships between levels of E_2 and memory functioning in men and women with AD. Emphasis was placed on everyday memory functioning, which is a major concern both for individuals with AD and their caregivers. The literature also provides suggestive evidence that DHEAS and CRT may be involved in the memory problems associated with AD, as discussed previously. Thus, in this study we recruited men, estrogen-using women and estrogen non-using women, all of whom had been diagnosed with AD, and compared their hormone levels and performance on tests of memory.

Hypotheses

Based on the review of the literature and the results of study 1, the following hypotheses were proposed: 1) Men and female estrogen-using AD patients would have higher E_2 levels than female estrogen non-using AD patients, 2) Performance on tests of verbal memory would be correlated with E_2 levels in the women, 3) Higher DHEAS would be associated with better memory performance in the AD patients, 4) Higher CRT levels would be associated with worse memory performance in the AD patients, 5) Women AD patients may have higher CRT levels than the men, 6) The ratio of DHEAS/CRT would be lower in female than male AD patients, 7) Lower

DHEAS/CRT ratios would be associated with poorer overall performance on the memory test battery, 8) Overall, female AD patients would evidence more profound verbal memory impairment than male AD patients.

Methods

Participants:

Patients with possible or probable Alzheimer's Disease who were being followed at the Memory Clinic of the Geriatrics department at the Jewish General Hospital return to the clinic annually for memory assessment and for molecular genetic studies. These Ss were referred by Dr. Howard Chertkow and Dr. Howard Bergman at the S.M.B.D. - Jewish General Hospital, Montreal, and screened for eligibility for the study. Exclusion criteria included the presence of medical conditions such as diabetes, recent heart attack, stroke and recent head injuries as well as use of any psychotropic medication and lack of fluency in the English language. The diagnosis of possible or probable AD was made by the neurologist based on the criteria established by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) of the National Institute of Health and the Alzheimer's Disease and Related Disorders Association (ADRDA), reported by McKhann et al. (1984), with the use of CT scans and blood work to rule out other sources of dementia. Charts were reviewed to determine the degree of dementia according to the Clinical Dementia Rating score, and only those diagnosed as mildly to moderately demented were included. Only patients assessed by clinicians as capable of giving their own informed consent were recruited, and not those under curatorship or judged by clinicians as not

legally able to give consent. For those patients taking estrogen replacement therapy, the duration and dosage of the prescription was verified by the caregiver and by having the S bring the pill container to the testing session whenever possible.

Materials:

The RBMT, previously described in Study 1, was used to assess everyday memory. Additionally, results of the WMS digit span (Wechsler, 1945), object naming (The Boston Naming Test; Kaplan, Goodglass & Weintraub, 1982), and the Mini-Mental Status Exam (Folstein, Folstein & McHugh, 1975), which were administered routinely by the neuropsychologist at the annual clinic visit were also obtained.

Procedure:

Patients with possible or probable Alzheimer's Disease being followed at the Memory Clinic return for annual assessments. At that time if, from a chart review, the patient appeared to meet the inclusion and exclusion criteria for the present study, he/she was approached by his/her physician and invited to participate. The study was explained to the prospective participant and to their caregiver and any questions answered by the research team, at which time informed consent was procured. The consent form was signed by the patient, their caregiver, the physician and by the research assistant who explained the study (Appendix E).

Then, a 10mL blood sample for hormonal assays was taken by the Memory Clinic nurse at the same time as blood was being collected for molecular genetic studies. The samples were placed on ice, centrifuged within two hours, and the plasma was stored at -50 degrees Celsius for assay at the conclusion of the study. The

patients and the caregiver then answered the same general information form as in Study 1, which collects information on sociodemographic status and personal, medical, psychological, educational and vocational history. This information was later checked for consistency with that on the patient's chart and his/her eligibility for the study reconfirmed. Next, the RBMT was administered with only the patient and experimenter present. The administration of the RBMT took approximately 30 minutes. Results of the other neuropsychological tests, usually administered within one week of the RBMT, as well as the Clinical Dementia Rating and the approximate date of AD onset, were obtained from the patients chart at a later date. Patients and/or their family members were reimbursed for travel and parking expenses.

Hormonal Assays:

Levels of E_2, T, CRT and DHEAS were measured at the conclusion of the study. The assays were performed at the same laboratory with the same kits as described in Study 1.

Results

Participants:

Twenty-six men, 19 estrogen non-using women, four estrogen past-using women and three estrogen-using women participated in this study. The estrogen past-users were indistinguishable from the non-users in terms of hormone levels, demographics and test scores, and therefore they were collapsed into the estrogen non-using group, for a total of 23 women. All subsequent analyses were performed with the past- and never-users together in the estrogen non-users group. All patients were

diagnosed with either mild or moderate, possible or probable dementia by a neurologist based on a full medical and neuropsychological assessment. Sociodemographic characteristics, duration of AD (based on the approximate date of onset obtained from each patients chart), age at onset and Clinical Dementia Rating (CDR) scores appear in Table 22.

Table 22
Sociodemographic Characteristics of AD patients

	Men (n=26)		Female Estrogen Non-Users (n=23)		Female Estrogen-Users (n=3)		Total Sample (n=52)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	75.62	7.58	75.88	8.09	77.73	3.97	75.85	7.56
Education (years)	10.65	3.49	10.41	3.61	10.67	0.58	10.55	3.40
Socioeconomic Status	48.14	51.42	51.42	15.62	49.03	4.62	49.61	14.27
AD[1] Duration (years)	4.49	2.62	3.54	1.72	4.20	0.20	4.06	4.20
Age at Onset (years)	71.97	7.45	72.70	7.75	75.53	4.14	72.39	7.3
CDR[2]	1.17	0.39	1.30	.057	1.33	0.58	1.24	0.48

no group differences
1. Alzheimer's Disease
2. Clinical Dementia Rating

The average CDR for the Ss was 1.24 (sd=0.48). On this measure, a score of 1 indicates mild dementia and a score of 2 denotes moderate dementia. The average duration of AD was 4.06 years (sd=2.20), the average age of all Ss was 75.85 years (sd=7.65), and the mean age at AD onset was 72.39 years (sd=7.30). The mean number of years of education was 10.55 (sd=3.4) and the socioeconomic status

(Blishen, 1967) was 49.61 (sd=14.27), indicating that the Ss were middle-class. There were no group differences in CDR scores, duration of AD, current age, age of AD onset, years of education or SES.

Hormonal Assays:

The hormone levels of the AD patients are presented in Table 23. Blood for radioimmunoassay was collected from all but one women estrogen non-user.

Table 23
Hormone Levels of AD Patients

Hormone	Men (n=26)		Female Estrogen Non-Users (n=22)		Female Estrogen-Users (n=3)	
	Mean	SD	Mean	SD	Mean	SD
Estradiol (pmol/L)	63.62[a]	21.18	27.01	27.01	91.00[b]	30.20
Testosterone (pmol/L)	44.68[c]	20.33	3.23	3.23	0.33	0.23
Cortisol (nmol/L)	325.31	112.41	303.05	109.76	266.33	40.20
DHEAS (umol/L)	2.53	1.87	2.14	1.85	0.70	0.30
DHEAS/Cortisol	8.39 E-6	6.25 E-6	7.13 E-6	6.20 E-6	2.79 E-6	1.62 E-6

a Men > E_2 than estrogen non-users ($p<.01$)
b Estrogen-users > E_2 than men, estrogen non-users ($p<.01$)
c Men > T than both female groups ($p<.001$)

One-way ANOVA analyses with Bonferroni-corrected post-hoc t-tests revealed that there were group differences in E_2 levels ($F[2,48]=31.33$, $p<.001$), such that the estrogen-users had higher levels than the men and the estrogen non-users ($p<.05$) and men had higher levels than estrogen non-users ($p<.05$). T levels were higher in the men compared with levels in both groups of women ($F[2,48]=48.66$, $P<.001$). There were no significant group differences in CRT, DHEAS or the DHEAS/CRT ratio.

Memory Performance:

Scores on the test battery are presented in table 24.

Table 24
Neuropsychological Test Scores - AD patients

Test Name	Max. possible score	Group					
		Men		Female Estrogen Non-Users		Female Estrogen-Users	
		Mean	SD	Mean	SD	Mean	SD
MMSE	30	20.74	4.19	19.25	4.93	19.00	10.44
Boston Naming	60	34.35	14.37	31.50	11.08	32.00	16.97
Digit Span	24	11.44	3.54	12.10	3.45	14.00	2.83
Forward	12	6.81	2.26	7.15	2.48	6.33	3.51
Backward	12	4.60	1.76	4.95	1.61	6.00	0.00
Name Recall	4	0.65	0.98	0.23	0.53	0.33	0.58
Belonging	4	1.50[a]	1.27	0.73	1.12	0.67	1.15
Appointment/Results	2	0.35	0.49	0.18	0.50	0.00	0.00
Picture Recognition	10	6.77	2.72	5.95	3.17	7.33	3.06
Story - Immediate	21	1.71[b]	1.56	1.02	0.94	0.83	0.76
Story - Delayed	21	0.56	0.97	0.09	0.29	0.50	0.87
Face Recognition	5	3.31	1.69	2.45	1.44	4.00	1.00
Route - Immediate	5	2.88	1.07	2.52	1.29	3.00	1.00
Route - Delayed	5	1.85	1.41	1.52	1.29	2.00	2.00
Message	6	3.00	1.41	2.52	1.33	3.00	1.00
Orientation	9	5.88	2.34	4.95	2.19	5.67	4.93
Date	2	0.50	0.86	0.45	0.86	1.00	1.00
RBMT Total	24	3.81[c]	3.16	2.00	2.64	4.00	2.65

a, b, c Men > Female estrogen non-users ($p<.05$)

One-way ANOVA analyses indicated no differences between the three groups on any of the neuropsychological tests, but due to the small sample size of estrogen-

users subsequent analysis was conducted excluding these three women. The group of men and the estrogen non-users group were compared with ANCOVA procedures, controlling for the level of depression as measured by the GDS, because GDS scores were elevated in some Ss (see mood results) and depressed mood can affect cognition. The men performed better than the estrogen non-using women on the tests of Belonging Recall (t=2.13, $p<.05$), Immediate Story Recall (t=2.32, $p<.05$) and on the RBMT Total score (t=2.21, $p<.05$).

Multiple stepwise hierarchical regression analyses were performed to confirm these sex differences, entering the variables of age, education, duration of AD and CDR first then forcing in gender, for the men and estrogen non-users. The same results were found, in that sex accounted for performance on Belonging Recall ($F[1,36]=5.80$, $R^2=.135$, $p=.02$), Immediate Story Recall ($F[1,36]=3.86$, $R^2=.091$, $p<.05$), and the RBMT Total Score ($F[1,36]=5.57$, $R^2=.126$, $p<.03$), beyond what was predicted by the other variables. Male gender was associated with better performance on these tests. The R^2 values reported represent the increment in variance accounted for by the gender variable. Thus, gender accounted for 13.5% of the variance in performance on Belonging Recall, 9.1% of the variance in Immediate Story Recall, and 12.6% of the variance on the RBMT Total Score.

Pearson product-moment correlations between hormone levels and cognitive test scores were calculated for the men and estrogen non-using women. Correlations were not performed for the estrogen-users, as the number of Ss in this group was too small. The results for the men are presented in Table 25, and for the estrogen non-using

women in Table 26.

Table 25
Correlations Between Hormone Levels and Test Scores - Male AD patients

Test Name	Male AD Patients (n=26)				
	E2	T	CRT	DHEAS	DHEAS/ CRT
MMSE	.277	.317	-.168	.270	.442
Boston Naming	.281	.161	.028	-.038	.117
Digit Span	-.005	.099	-.105	.048	.137
Forward	.023	.060	-.008	.145	.161
Backward	.011	.161	-.199	-.115	.043
Name Recall	.124	.484**	.088	.159	.272
Belonging	.039	.347	.192	.146	.180
Appointment/Results	.522*	.342	.015	.157	.252
Picture Recognition	-.206	-.116	.310	.150	.062
Story - Immediate	.107	.103	-.008	.121	.173
Story - Delayed	-019	.056	-.027	.034	.187
Face Recognition	-.193	-.065	.474**	.205	.023
Route - Immediate	.210	-.060	-.095	-.009	.069
Route - Delayed	.378	.085	-.273	.035	.161
Message	.225	.043	-.088	-.037	.041
Orientation	.244	.483**	.144	.333	.312
Date	.081	.026	.356	.086	-.040
RBMT Total	-.072	-.006	.193	.025	.012

* p<.01
** p<.02

Table 26

Correlations Between Hormone Levels and Test Scores - Female Estrogen non-using AD patients

Test Name	Estrogen non-using Female AD Patients (n=21)				
	E2	T	CRT	DHEAS	DHEAS/ CRT
MMSE	-.145	.392	-.178	.023	-.070
Boston Naming	-.017	-.167	.589*	.161	-.100
Digit Span	-.210	.364	-.192	.438	.308
Forward	-.173	.387	-.112	.362	.244
Backward	-.177	.172	-.235	.372	.270
Name Recall	-.146	-.283	-.098	.241	.277
Belonging	-.372	.400	-.100	-.379	-.387
Appointment/Results	-.021	.619*	.064	-.108	-.117
Picture Recognition	-.627*	.251	-.013	-.120	-.317
Story - Immediate	.042	.134	-.208	.230	.260
Story - Delayed	-.018	.506**	-.028	.155	.172
Face Recognition	-.321	-.017	-.016	-.123	-.259
Route - Immediate	-.451	.179	-.285	.250	.181
Route - Delayed	-.629*	.076	-.180	.029	-.046
Message	-.342	.030	.101	-.358	-.454
Orientation	-.291	-.008	.303	.076	-.110
Date	-.563*	-.059	-.040	-.371	-.385
RBMT Total	-.729*	.112	-.035	-.306	-.385

* $p<.01$
** $p<.02$

Cutoff values of $p<.01$ were used for these correlations to control for the large number of correlations performed. Correlations between $p<.02$ and $p<.01$ will be

discussed with caution. In the men, E_2 levels were positively associated with scores on remembering an appointment (r=.522, p<.01), and higher T levels were related to higher scores on Name Recall (r=.484, p=.014) and Orientation (r=.483, p=.015). As well, CRT levels were positively associated with Face Recognition scores (r=.474, p=.017) in these men with AD.

In the women estrogen non-users (Table 27), E_2 levels were negatively correlated with a number of tests, including Picture Recognition (r=-.627, p<.002), Delayed Route memory (r=-.629, p<.003), ability to recall the proper Date (r=-.563, p<.008), and the RBMT Total score (r=-.729, p<.001). T levels were positively associated in these women with performance on remembering an Appointment (r=.619, p<.003) and Delayed Story Recall (r=.506, p<.019), and higher CRT levels were associated with better performance on the Boston Naming Test (r=.589, p<.01).

Low Vs. High Hormone Groups:

Since there were no group differences between levels of DHEAS, CRT and the DHEAS/CRT ratio, the Ss were divided, using a median split, into high and low groups for each of these hormone levels. The mean scores of the high vs. low groups on each of the cognitive tests were then compared using independent samples t-tests. The results of these comparisons can be found in Table 27.

Ss in the High DHEAS group performed better than those with lower DHEAS levels on the tests of Name Recall (t=2.48, p<.02), Digits Total (t=2.03, p<.05) and Forward (t=2.27, p<.05), and also had marginally higher MMSE scores (t=1.98, p=.054). Those with lower CRT levels performed better on the Delayed Route Recall

Table 27

Cognitive Test Scores: Low Vs. High Hormone Levels in AD Patients

Test Name	Low DHEAS (n=26)	High DHEAS (n=24)	Low CRT (n=25)	High CRT (n=23)	Low DHEAS/ CRT	High DHEAS/ CRT
CDR	1.25	1.24	1.26	1.25	1.10	1.39[f]
MMSE	18.67	21.52[a]	20.04	19.70	19.75	20.00
Boston Naming	32.78	33.33	30.00	36.25	36.79	29.83
Digit Span Total	10.96	12.95[b]	11.71	11.95	11.57	12.10
Forward	6.24	7.74[c]	6.68	7.24	6.71	7.18
Backward	4.58	5.14	4.88	4.65	4.70	4.86
Name Recall	0.19	0.75[d]	0.48	0.43	0.24	0.70
Belonging	1.00	1.29	1.20	1.00	1.24	0.96
Appointment/Results	0.19	0.33	0.16	0.35	0.24	0.26
Picture Recognition	6.46	6.50	6.48	6.39	7.04	5.78
Story Recall - Immediate	1.15	1.60	1.28	1.50	1.26	1.52
Story Recall - Delayed	0.27	0.46	0.40	0.30	0.32	0.39
Face Recognition	2.81	3.25	2.76	3.26	3.32	2.65
Route - Immediate	2.60	2.95	2.92	2.57	2.68	2.82
Route - Delayed	1.80	1.67	2.17	1.22[e]	1.76	1.64
Message	2.96	2.71	2.83	2.91	3.08	2.64
Orientation	5.08	6.04	5.40	5.60	5.40	5.61
Date	0.62	0.42	0.52	0.57	0.72	0.35
RBMT Total	3.15	3.04	3.24	2.91	3.48	2.65

a, b, c, d High DHEAS > Low DHEAS, $p<.05$
e Low CRT > High CRT, $p<.05$
f High DHEAS/CRT > Low DHEAS/CRT, $p<.05$

task (t=2.47, p<.02) than the Ss in the upper range of CRT values, and finally, Ss with a higher ratio of DHEAS/CRT had a slightly higher CDR (t=-2.09, p<.05), indicating that they were more demented than those with a lower ratio. No corrections for multiple comparisons were made on this preliminary analysis, which will therefore be interpreted with caution.

Mood Scores:

GDS Scores were available for 24 of the men, 19 of the estrogen non-using women and two of the estrogen-users. Out of a total possible score of 30, where higher scores indicate more depressive symptoms, the mean scores were 7.75 for the men, 10.0 for the estrogen non-users, and 7.00 for the estrogen users. Overall, the mean was 8.67 (sd=4.41). With scores from only two estrogen-users, statistical comparisons between all three groups were not possible, therefore scores of the men and estrogen non-using women on the GDS were compared using t-tests. Between the men and estrogen non-users there were no group differences in mood scores.

Scores between 0 and 10 fall into the normal, non-depressed range of the GDS, whereas scores over 11 indicate some depression (Yesavage, 1986). GDS scores over 14 resulted in 100% specificity in classifying non-demented elderly men and women as meeting Research Diagnostic Criteria for mild depression in the normative sample (Yesavage et al., 1983), and in a sample of 43 demented elderly men and women, those who were classified as not depressed received a mean score of 7.49. In our sample of men, sixteen Ss scored below 10, six scored between 10 and 14, and two

scored above 14. In the estrogen non-users, ten Ss scored below 10, six were between 10 and 14, and three scored above 14. Both of the estrogen-users scored below 10. This indicates that five of our Ss showed mild depression, 12 of them had some depressive symptoms and 28 were non-depressed. As depression can impact cognitive function, the GDS score was used as a covariate in the cognitive analyses.

Discussion

Hormone Levels

As expected, the women estrogen-users had higher levels of E_2 than both the men and the non-users, and the men had higher levels of E_2 than the estrogen non-users. As well, the men had higher T levels than both groups of women. However, there were no gender differences in DHEAS or CRT levels or in the ratio of DHEAS/CRT in these AD patients. Based on the endocrine norms (Table 4), it was expected that DHEAS levels would be higher in the men than the women. In terms of absolute values (Table 23), the estrogen-users did have lower DHEAS levels than the men (0.7 vs. 2.53 umol/L), but perhaps due to the small sample size this difference was not statistically significant. These findings are consistent with Nasman et al. (1990), who found no gender differences in DHEAS levels between 78 year-old demented women and men. However, in that study the groups of men and women were comprised of some cases of AD and some cases of multi-infarct dementia, so those results do not reflect DHEAS levels in AD patients alone.

The lower limit of the normal male range of DHEAS levels is 5.4 umol/L. Considering that in our study the male AD patients had DHEAS levels of 2.53 umol/L,

less than half the lower limit, it is not surprising that these levels are not higher than the women's. In fact, both the men and the women AD patients had low DHEAS levels compared to the norms, which supports the contention that AD patients have lower than average DHEAS levels (Sunderland et al., 1989). However, our norms do not specify the ages that are included in the male range, and it may be that few elderly individuals were used in constructing that range.

Based on the findings of Leblhuber et al. (1993), we predicted that the women AD patients would have elevated CRT levels compared to the men. However, no such gender differences were evident. In the Leblhuber et al. (1983) study the AD Ss were far more severely demented than ours (MMSE scores of 5.2 vs. 20, respectively). If it is true that more severe dementia is associated with CRT hypersecretion, then this difference could account for the increased CRT levels in those women. The finding of higher CRT in more severely demented women is consistent with the glucocorticoid cascade hypothesis wherein HPA dysregulation leads to CRT hypersecretion, subsequent neuronal death in the hippocampus and resultant dementia (Sapolsky et al., 1986). If this dysregulation process is more likely to occur in women, that could also help to account for the greater incidence of AD in women than in men (Jorm et al., 1987; Rocca et al, 1986; Keefover, 1996), which can only partially be explained by demographic and social factors (Kay, 1986).

Neither were there any significant group differences in the ratio of DHEAS/CRT. Svec & Lopez-S (1989) theorized that women with AD might show a lower ratio of DHEAS/CRT, based on the findings that AD patients had lower DHEAS

than controls (Sunderland et al. 1989) and the generally lower DHEAS concentrations in elderly women. However, other researchers who have actually calculated this ratio in clinical investigations failed to find gender differences in AD patients, although they did report a higher DHEAS/CRT ratio in AD versus control women (Leblhuber et al. 1993). If the ratio of DHEAS/CRT were a valid measure of protection to degeneration in the hippocampus, one might expected it to correlate with degree of dementia in AD patients, but this failed to occur both in this study and in the Leblhuber et al (1993) report. In fact, the estrogen-using women had the lowest ratio of DHEAS/CRT and, if anything, they performed better than the men and estrogen non-users on the cognitive tests. Thus, as in the healthy elderly study, this measure appears to have questionable predictive validity in AD patients.

Neuropsychological Tests

The major neuropsychological test results of this study were that the male AD patients scored higher than the female estrogen non-using patients on Immediate Story Recall, Remembering a Belonging and the RBMT Total score. This occurred despite the fact that both groups had similar CDR scores and duration of AD, and depression scores were used as a covariate in the analyses. Others have also reported that women with AD performed worse than men on tests of object naming, verbal fluency and delayed verbal recall (Henderson & Buckwalter, 1994) and naming and word recognition (Ripich et al., 1995) after controlling for education, age and dementia severity. Considering that the elderly men had higher E_2 and T levels than the estrogen non-using women, that T is converted to E_2 in the brain (MacLusky et al.,

1987) which causes hippocampal neuronal growth (Wooley & McEwen, 1992), it is possible that the male hippocampus is protected from aging by their higher E_2 levels. It also follows that the degeneration of hippocampal neurons characteristic of AD pathology (West et al., 1994), and the decline in cognitive functions subserved by that structure (Squire, 1992) may be less severe in those who retain higher levels of E_2 with age, namely, men and estrogen-using women. Indeed, the estrogen-using women in this study, though few in number, did perform better in absolute terms than the estrogen non-using women on the majority of the tasks (Table 25), although these differences were not statistically significant.

The findings from this study suggest that E_2 may retard the neural degenerative processes that result in severe memory deficits in patients with AD. It is also tempting to speculate that the 2:1 female to male ratio in the incidence of AD (Rocca, Amaducci & Schoenberg, 1986; Jorm et al., 1987) may be due, in part, to the fact that male hippocampi are protected to some degree by their lifelong exposure to estrogen. Indeed, recent epidemiological studies found a lower incidence of AD in female estrogen-users compared to non-users (Henderson, et al., 1994; Paganini-Hill & Henderson, 1994; Tang et al., 1996; Kawas et al., 1997), and a dose-response relationship where higher doses of E_2 and longer durations of ERT were related to lower chances of developing AD (Tang et al., 1996; Paganini-Hill & Henderson, 1994). Additionally, in preliminary clinical trials, exogenous estrogen enhanced memory in women with AD (Honjo et al., 1989; Fillit et al., 1986; Ohkura et al., 1994). ERT may also delay the onset of AD, as observed in a recent prospective

epidemiological study (Tang et al, 1996). Indeed, although the age of AD onset was not statistically different among our groups, the average age of onset for the estrogen-users was 75.5 years, compared with 72.0 years for the men and 72.7 years for the estrogen non-using women. This difference in age of onset in the estrogen-users of approximately three years supports the contention of Tang et al. (1996) that estrogen-use may delay the onset of AD in women.

Ss with low CRT performed better on the Delayed Route Recall task compared to those with high CRT. This is consistent with the findings from Study 1 in which healthy elderly men and women with lower CRT levels performed better on a number of verbal memory tasks. However, the group differences here were not found on the verbal memory tasks, as in Study 1, but on Delayed Route Recall, a task that correlated with Visual Reproduction in Study 1, which suggests that this task measures visuo-spatial ability. Other studies have found impaired performance on maze learning in rats (Landfield et al., 1981), and visual/spatial memory in humans (Mauri et al., 1993; Starkman et al, 1992) after CRT administration. However, while some human studies have found effects of higher CRT levels exclusively on verbal memory , (Lupien et al, 1994; Wolkowitz et al, 1990), none have reported only spatial memory deficits prior to our findings. The verbal tasks, particularly remembering a story, were very difficult for these patients with AD and their mean scores were low with very little variability. Thus, the floor effect in the performance of the AD patients on these verbal memory tasks may have precluded the possibility of discovering similar verbal memory differences between low and high CRT groups as were seen in Study 1 in healthy

elderly.

When Ss were grouped by a median split into low and high DHEAS groups, the group with high DHEAS levels performed better than the group with low levels on four different tasks, Digits Total and Forward, Name Recall and the MMSE, although the low DHEAS group were not more demented as assessed by the CDR. This association of DHEAS with better memory is consistent with findings that DHEAS administration caused neuronal sprouting in the rat hippocampus (Roberts et al., 1987) and positive health outcomes such as improved immune functioning (Morales et al., 1994; Yen et al., 1995) and lower rates of cardiovascular disease (Barrett-Connor et al., 1986) in humans. An inverse relationship between DHEAS levels and the presence of dementia occurred in male nursing home residents (Rudman et al., 1990), but the sample in that study consisted of mixed etiology dementia syndromes. In a study of three men and three women with major depression, DHEAS administration resulted in improvements of mood and of "automatic" memory processing, but not explicit verbal recall tasks (Wolkowitz et al., 1997). In that study, DHEAS levels were correlated with decreases on the Hamilton Depression Rating Scale subscale items assessing "cognitive disturbance". These results support the possibility that DHEAS helps to maintain certain memory functions. Possible mechanisms for this action include DHEAS inhibition of GABA (Majewska, 1994) and glucocorticoids (Svec & Lopez-S, 1989) in the hippocampus.

It is important to note that plasma RIAs of DHEAS may not accurately reflect levels of this steroid in the brain, where they may be many times higher (Majewska,

1995). Indeed, it is questionable whether correspondence exists between plasma DHEAS levels and brain levels, since higher plasma concentrations of DHEAS have been reported in males compared to females (Vermeulin, 1995), but post-mortem studies in the brain have found higher levels in females rather than males (Lanthier & Patwardhan, 1986). Our knowledge of the exact nature of the relationship between peripheral plasma levels of DHEAS and brain levels of the hormone awaits further comparative research. Meanwhile, it is important to acknowledge that steroid levels measured from peripheral blood plasma may not be 100% accurate in reflecting brain activity. This holds for the other steroid hormones as well, since the degree of correspondence between peripheral plasma levels and brain levels is generally unknown.

Hormone-Test Score Correlations

Because of the small number of estrogen-users with AD (n=3), correlations between hormone levels and memory performance were performed only for the men and the estrogen non-using women. In the men, E_2 levels were positively associated only with remembering an appointment. Remembering an appointment was one of the most difficult tasks in the battery for both healthy elderly Ss and AD patients, and most AD Ss received a score of zero. In male rats, E_2 enhanced performance in both young and aged rats in trials that required a delay component and were more difficult, but not on immediate trials which were easier (Luine & Rodriguez, 1994). This suggests that, in men, E_2 may serve to enhance performance on more difficult tasks rather than on simpler ones.

To our knowledge, no other studies have measured E_2 levels in elderly men with AD. However, in healthy young men, E_2 levels were correlated with visuo-spatial performance (Kampen & Sherwin, 1996). Because a purely visuo-spatial test was not included in our battery, a direct comparison with this finding in young men is not possible. Remembering an Appointment, the one test that correlated positively with E_2 in the men, isn't obviously either verbal or visual in nature - the instructions are delivered aloud verbally by the experimenter, and the cue to remember the appointment is an auditory beep.

Scores of the women estrogen non-users showed an opposite pattern of correlations to the men, in that they were negatively associated with E_2 levels on a number of tests. This is contrary to what would have been expected if E_2 had enhancing effects on memory. However, the levels of E_2 in this sample of untreated women with AD were extremely low, and showed little variability. In addition, there were a number of women who scored zero on all the subtests that showed negative correlations, and they also had relatively high E_2 levels, thus accounting for the negative correlations. It is unlikely that such low circulating E_2 values would influence cognition. Other studies have failed to find correlations between E_2 and cognition in postmenopausal women with extremely low E_2 levels (Kampen & Sherwin, 1994).

Sample Characteristics

One obvious criticism of this study is the small number of estrogen-using women with AD. It would have been ideal to have a much larger group of these individuals, but it was difficult to find AD patients who were taking estrogen. The

overall incidence of estrogen-use in this elderly and cognitively impaired sample was very low, which has been confirmed in larger epidemiologic studies investigating estrogen-use and AD (Henderson et al., 1994; Tang et al., 1996). Few of these 75 year-old women started using estrogen at their menopause, an average of 25 years ago, when such treatment was relatively uncommon. As well, in general physicians may be less likely to prescribe what is sometimes considered a "quality of life" medication to women suffering from AD, or ERT may be discontinued when a diagnosis of AD is made.

It is clear that a larger comparison group of estrogen-using AD patients would have allowed us to better address issues regarding the cognitive performance and hormone levels in individuals with AD. Because of the small number of estrogen-using women with AD, and the possible treatment biases in naturalistic populations, prospective long-term trials are necessary to fully elucidate the effects of estrogen administration on cognition in women with AD. The ideal study would be a large-scale blinded treatment trial of estrogen in AD patients, who would be randomly assigned to estrogen or placebo, with a washout period and crossover to the other treatment. Such a study would allow experimental control over the dosage, route of administration and duration of E_2 use. Additionally, pre- and post-treatment cognitive testing would be possible. Such a multi-site, clinical trial of E_2 in patients with AD is currently underway (Kuller, 1996).

Summary

Men with AD performed better than estrogen non-using women with AD on

a number of everyday memory tests, namely, Delayed Story Recall, Remembering a Belonging and the RBMT Total score, concomitant with their higher E_2 and T levels. The small sample of estrogen-users performed similarly to the men on most tests, and frequently better than both the men and estrogen non-users, although these differences were not statistically significant, probably due to the small size of the estrogen-using group. Possible explanations of these results are based on the effects of E_2 on hippocampal morphology (Gould et al., 1990), neurochemistry (Luine, 1985), and nerve growth factor (Toran-Allerand et al., 1992).

AD patients with higher DHEAS levels performed better on Digits Total and Forward, Name Recall and the MMSE than those with lower DHEAS levels, although they were not more demented as assessed by the CDR. The CDR is a very gross measure of dementia, and likely to be less sensitive than the MMSE to small fluctuations in dementia severity, since the MMSE has a much larger range of possible scores. Based on the MMSE scores, patients with higher DHEAS levels showed less overall cognitive impairment. These results support the notion that DHEAS enhances cognition, which could occur via the ability of this hormone to block GABA activity in the hippocampus (Majewska, 1995), and/or antagonize the detrimental hippocampal effects of glucocorticoids (Svec & Lopez-S, 1989).

Patients with lower CRT levels performed better on Delayed Route Recall, a measure of spatial memory, than those with higher CRT levels. The finding that higher CRT levels were detrimental to an aspect of everyday memory supports the results of Study 1, in which higher CRT levels were detrimental to verbal memory

performance in healthy elderly men and women, and extends this finding to AD patients.

Comparisons between the hormone levels of these AD patients and other study samples suggest that there may be differences in the patterns of hormone secretion between patients with mild to moderate AD, and in those who are more severely demented. In one sample of more severely demented patients, the women with AD had higher CRT levels than the men (Leblhuber et al., 1993), which was contrary to our finding of similar CRT levels between groups of mildly demented men and women. This supports the idea that with the progression of the disease, HPA dysregulation may occur.

The results of this study helped to clarify some of the gender differences present between men and women with AD, both in the area of memory function and hormone levels. These findings suggest that higher circulating E_2 may be related to better cognitive performance, as observed in the men and the women estrogen-users compared to the estrogen non-users. Additionally, DHEAS may enhance memory in AD patients, while higher CRT levels may be detrimental to some aspects of cognition in this population.

Study 3: - Hormone Levels and Everyday Memory Performance of AD Patients Compared to Healthy Elderly Controls.

Introduction

In addition to investigating the relationships between hormones and memory functions in AD patients, we sought to compare their values and performance to age-matched cognitively unimpaired control subjects. The following hypotheses were proposed based on the review of the literature: 1) The AD patients would perform worse on all cognitive tests than controls, 2) AD patients would have lower levels of DHEAS compared to controls, 3) AD patients (both male and female) would have lower E_2 levels than age-matched controls, 4) Female AD patients would have higher CRT levels than controls, and 5) AD patients would show more depressive affect than controls.

Methods

Participants:

The 52 AD patients from Study 2 were matched with 52 healthy elderly Ss from T2 of Study 1. The healthy elderly control Ss were selected from the group who completed T2 of study 1 on the basis of age, education, gender and estrogen status in an attempt to create groups that were matched with the AD patients on these variables. The final healthy elderly control group consisted of 23 men, 23 estrogen non-using women and six estrogen-users.

Materials:

All AD patients and healthy elderly control Ss had been tested using the

RBMT, Digit Span and the GDS.

Procedures:

Test scores of healthy elderly control Ss who were chosen as a matched sample for this study were taken from their T2 scores in Study 1, and compared to that of the AD patients in Study 2.

Hormonal Assays:

Assay results for E_2, T, CRT and DHEAS levels collected at T2 of Study 1 and in Study 2 were used in this study.

Results

Participants:

The demographic characteristics of the AD patients and the Control group are presented in Table 28. Overall, the groups were matched on age and SES, but the control Ss had more years of education than the AD patients ($t=2.63$, $p=.01$). Independent samples t-tests indicated that the control men were of higher education than the AD men ($t=2.12$, $p=.039$), but there were no significant group differences on years of education in the women.

Hormonal Assays:

Hormone levels for the AD patients and controls, according to gender and group are presented in Table 29. Differences in hormone levels between the controls and AD patients were investigated by performing a group by gender ANOVA analyses. There were no interactions between group and gender, and no main effects for group. Thus none of the hormone levels were different between the AD patients

and controls.

Table 28
Sociodemographic Characteristics of AD patients vs. Controls

Group	Age (years)		Education (years)		Socioeconomic Status^	
	Mean	SD	Mean	SD	Mean	SD
AD Patients (n=52)	75.85	7.56	10.55	3.40	49.61	14.27
Men (n=27)	75.62	7.58	10.65	3.49	48.14	15.24
No-E Women (n=22)	75.88	8.09	10.41	3.61	51.42	14.16
E-Women (n=3)	77.73	3.97	10.67	0.58	49.03	4.62
Controls (n=52)	74.22	5.42	12.25[a]	3.40	54.80	14.11
Men (n=23)	73.37	5.88	12.78[b]	3.61	48.14	15.24
No-E Women (n=23)	74.83	5.14	11.30	2.34	51.42	14.16
E-Women (n=6)	75.11	4.98	13.83	2.79	49.03	4.62

a Controls overall > Education than AD patients, p=.01
b Male Controls > Education than male AD patients, p<.05

However, there was a main effect for gender on levels of E_2 ($F[2,90]=51.52$, $p<.0001$), T ($F[2,90]=110.02$, $p<.0001$), DHEAS ($F[2,90]=8.03$, $p<.001$) and DHEAS/CRT ($F[2,90]=5.81$, $p<.005$). When probed with Bonferroni corrected post-hoc t-tests, overall, the estrogen-users had higher E_2 than the men and non-users, and the men had higher levels than the estrogen non-users. The men had higher T and DHEAS levels than both groups of women, and the men also had a higher ratio of DHEAS/CRT than

the estrogen-users, but not the estrogen non-users. The hormone levels for the AD patients and controls are presented in Figures 6-10

Table 29
Mean Hormone Levels of AD Patients vs. Controls

	E_2 [a]	T[b]	CRT	DHEAS[b]	DHEAS/CRT[c]
AD Patients - overall	50.00	24.61	312.61	2.26	.75
Men (n=26)	65.26	44.68	325.31	2.53	.84
E non-users (n=21)	27.10	3.23	303.05	2.12	.71
E-users (n=3)	91.00	0.33	266.33	0.70	.28
Controls - overall	55.51	16.58	345.79	2.42	.73
Men (n=22)	66.45	34.35	376.95	3.38	.98
E non-users (n=20)	26.48	1.93	336.16	1.89	.61
Estrogen-users (n=6)	112.17	0.25	262.00	0.68	.26

AD vs. Control: no group differences on any hormones

E2

a Estrogen-users > men, estrogen non-users
Men > estrogen non-users

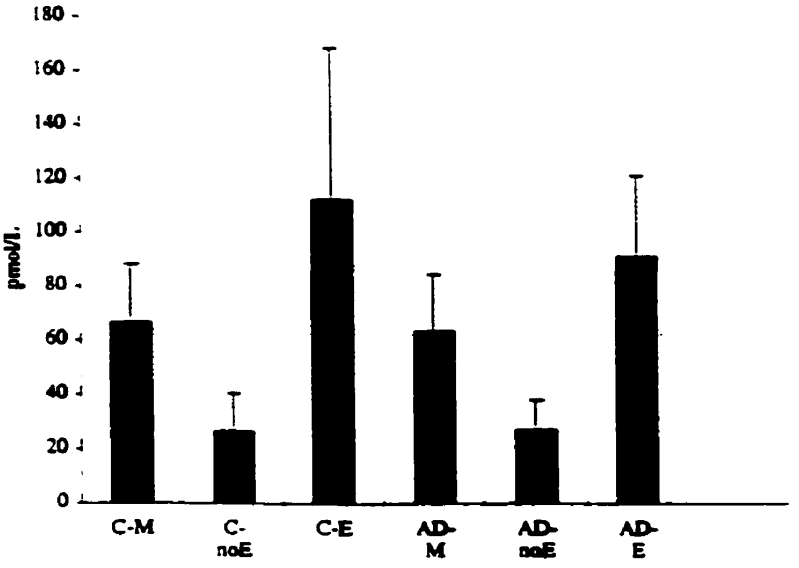
T, DHEAS

b Men > all groups of women

DHEAS/CRT

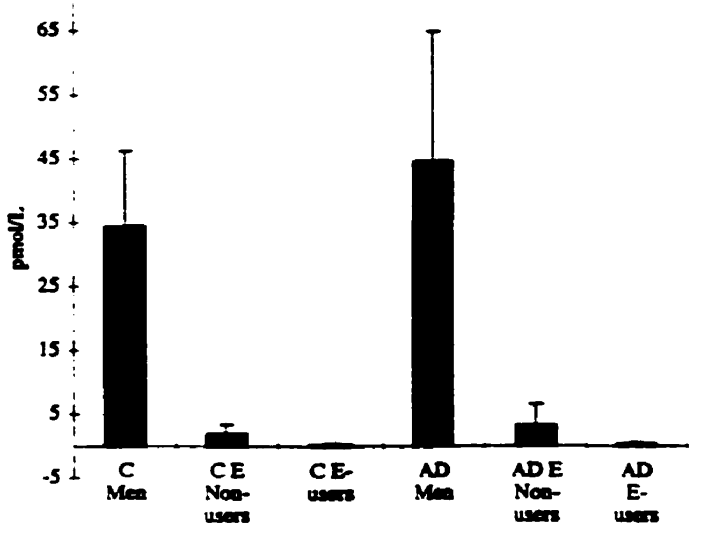
c Men > estrogen-users

Figure 6 - Estradiol Levels



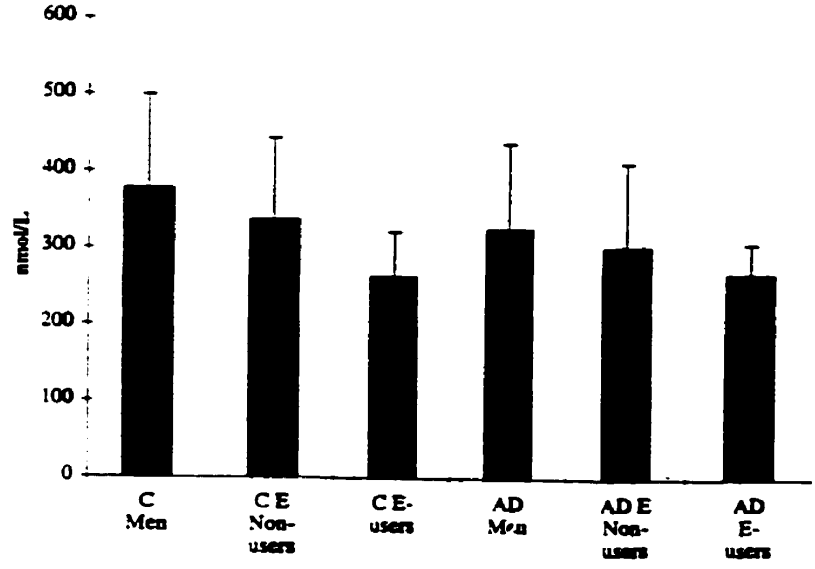
Estrogen-users higher than men and non-users ($p<.001$)
Men higher than estrogen non-users ($P<.001$)

Figure 7 - T Levels



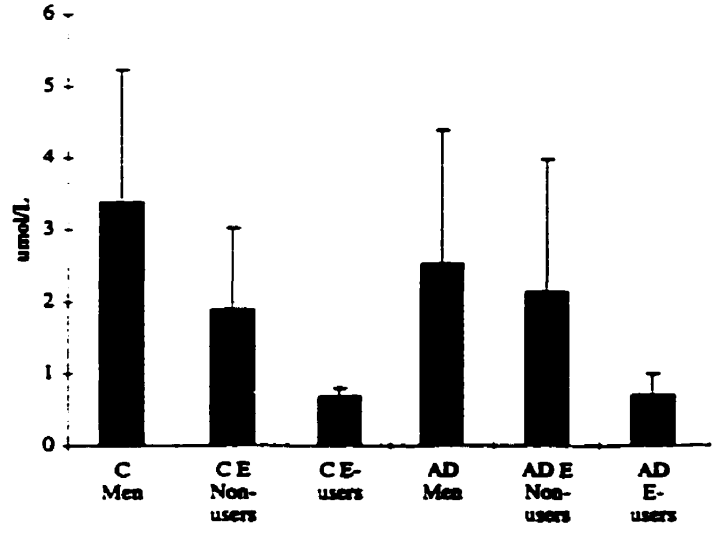
Men higher than women ($F[2,95]=111.88$, $p<.0001$)

Figure 8 - Cortisol Levels



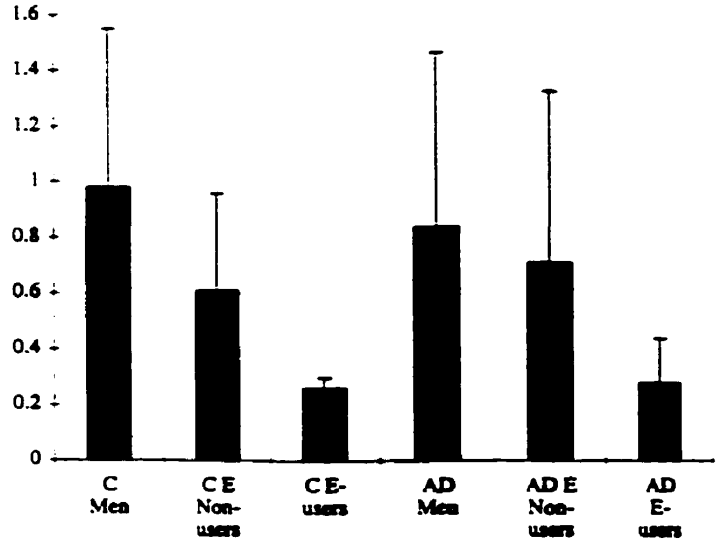
No group differences

Figure 9 - DHEAS Levels



Men higher than Women ($F[2,96]=8.16$, $p<.001$)

Figure 10 - DHEAS/CRT Ratios



Men higher than estrogen-users ($F[2,93]=6.23$, $p<.005$)

Memory Tests

There were significant group differences on the scores of the memory tests that were administered to both AD patients and controls and presented in Table 30. As expected, overall the control group performed significantly better than the AD patients even after controlling for years of education with multivariate ANCOVA procedures ($p<.001$). The factoring out of educational level before conducting group comparisons resulted in adjustments in the means of only the Immediate ($p<.001$) and Delayed ($p<.05$) Route scores and the RBMT Total Score ($p<.05$).

The performance of the AD patients compared to the healthy elderly controls was the worst on the RBMT Total score ($F[1,100]=424.5$), Name Recall

Table 30

Neuropsychological Test Scores - AD patients vs. Controls

Test Name	Max. possible score	AD Patients		Controls	
		Mean	SD	Mean	SD
Digit Span	24	11.77	3.43	15.56*	3.79
Forward	12	6.90	2.36	8.67*	2.14
Backward	12	4.77	1.68	6.98*	2.17
Name Recall	4	0.45	0.81	3.01*	1.19
Belonging	4	1.10	1.25	3.31*	0.54
Appointment/Results	2	0.23	0.47	1.44*	0.75
Picture Recognition	10	6.45	2.91	9.58*	1.00
Story - Immediate	21	1.29	1.30	7.08*	3.18
Story - Delayed	21	0.30	0.71	5.68*	3.12
Face Recognition	5	2.92	1.56	4.71*	0.54
Route - Immediate	5	2.72	1.16	4.21*	0.89
Route - Delayed	5	1.70	1.36	4.13*	0.79
Message	6	2.78	1.31	5.08*	1.15
Orientation	9	5.44	2.34	8.85*	0.36
Date	2	0.51	0.86	1.92*	0.39
RBMT Total	24	2.98	2.87	17.59*	3.62

* Control > AD, $p<.001$

($F[1,100]=144.5$), Remembering a Belonging ($F[1,100]=115.4$), Delayed ($F[1,100]=113.9$) and Immediate ($F[1,100]=111.5$) Story Recall, and Delayed Route ($F[1,100]=107.7$). In contrast, although they did significantly worse than the controls,the performance of the AD patients was least impaired on Forward

(F[1,100]=12.6), Total (F[1,100]=24.1) and Backward (F[1,100]=25.9) Digit Span, Immediate Route recall (F[1,100]=45.9), and on Picture (F[1,100]=50.1) and Face (F[1,100]=52.5) Recognition.

Mood Scores

The AD patients scored an average of 8.67 on the GDS, out of a possible total score of 30, where higher scores indicate more depressive symptoms. This was significantly higher than the control group's mean score of 3.98 (t=5.41, p<.001). When hormone and gender groups were examined using one-way ANOVA analyses with Bonferroni corrected post-hoc t-tests, group differences were found (F[5,88]=7.22, p<.0001), such that the AD female estrogen non-users scored higher than all three control groups (10.00 vs. 3.38, 4.80 and 3.20) on the GDS, and the AD men scored higher than the control men (7.75 vs. 3.38). There were no significant differences between the AD estrogen-users (mean 7.00) and the control estrogen-users (mean 3.20) on this measure, which may have been due to small sample sizes.

An item analysis of the individual GDS items was undertaken to determine which statements the AD patients preferentially endorsed compared to the controls. Mann-Whitney U-tests on each GDS item showed that overall the AD patients were more likely than the controls to confirm that they felt their life was empty (p<.02), often got bored (p<.002), didn't find life very exciting (p<.005), were not in good spirits most of the time (p<.01), often felt downhearted and blue (p<.005), frequently felt like crying (p<.05), often felt helpless (p<.01), felt worthless the way they are now (p<.005), found it hard to get started on new projects (p<.05), had recently dropped

many of their activities and interests ($p<.002$), didn't feel full of energy ($p<.05$), felt that most people were better off than they were ($p<.05$), had more problems with memory than most ($p<.001$), found it hard to make decisions ($p<.005$) and felt their mind was not as clear as it used to be ($p<.001$). In contrast, there were no group differences between the AD patients and healthy elderly controls in basic satisfaction with their life, being hopeful about the future, being afraid that something bad is going to happen to them, feeling happy most of the time, thinking its wonderful to be alive now, feeling that their situation is hopeless, being bothered by thoughts they can't get out of their head, getting restless and fidgety, worrying about the future, worrying about the past, getting upset over little things, having trouble concentrating, enjoying getting up in the morning or avoiding social gatherings.

Subsequent factor analysis revealed three factors that accounted for 35.4% of the variance. The first factor, accounting for 19.6% of the variance, loaded heavily on items indicative of dysphoria, such as feeling downhearted and blue, upset and teary. The second factor, accounting for 8.6% of the variance, included positively endorsed outlook items such as feeling hopeful about the future, feeling it is wonderful to be alive and enjoying getting up in the morning. The third factor contained items related to mental acuity such as ease in decision making, feeling clearheaded, concentrating and having memory problems and accounted for 7.2% of the variance. The AD patients were more likely to endorse the dysphoric items and not endorse the mental acuity items (i.e. they endorsed mental dullness items) than were the healthy elderly controls, but they were no more likely to have a negative outlook on life than the

controls.

Discussion

Hormone Levels

The comparison of healthy elderly control Ss and AD patients provided some information on differences in endocrine status between these two groups. Contrary to what was hypothesized, there were no overall group differences between AD patients and controls in levels of any of the hormones we measured. Some authors have speculated that estrogen levels may be lower in women with AD compared to controls, and used body weight as an indirect marker of estrogen levels (Birge, 1996; Henderson, 1995). This is based on the fact that, after the menopause, much of the estrogens in circulation are peripherally converted from androgens in fat tissue. Therefore, higher body weight has been identified as an indicator of higher estrogen levels. Thus, the observation that women with AD were of lower body weight than controls (Berlinger & Potter, 1991; Buckwalter, Schneider & Dunn, 1994) led to the assumption that they also had lower estradiol levels, although circulating E_2 was not assayed. However, in our study E_2 levels were not lower in AD patients compared to controls. The idea that current circulating levels of endogenous E_2 reflect cognitive status is not supported by the data in the present study. Clearly, a more complicated interaction between risk factors for AD, effects of aging on the central nervous system, individual factors, and peripheral effects of E_2 that potentially effect cognitive functioning need to also be considered.

Another theory holds that greater cumulative lifelong exposure to estrogens

affords increased protection against dementia in elderly women. This theory has been supported by epidemiological studies that showed a dose-response effect of cumulative estrogen-exposure on the odds ratio for developing AD (Paginini-Hill & Henderson, 1994; Tang et al., 1996). The effects of E_2 on the hippocampus are rapid and transitory in adult female rats, with fluctuations in spine density occurring over the estrous cycle (Wooley & McEwen, 1992). Within a short time period after OVX, decreases in hippocampal spine density occur, which are quickly restored to pre-OVX densities with E_2 administration (Gould et al., 1990). However, upon withdrawal of estrogen treatment, hippocampal neurons quickly return to post-OVX spine density values (Gould et al., 1990). These findings from basic neuroscience therefore do not support the theory that past estrogen use or cumulative estrogen exposure would be as important as currently circulating E_2 levels in influencing hippocampal morphology, and thus, memory functions. Indeed, when our four AD patients who were past estrogen-users were compared to the never-users, their cognitive test scores and all hormone levels were indistinguishable.

Levels of circulating E_2 were not different between the AD patients and controls in the present study, and E_2 levels were not correlated with cognitive performance in these AD patients. Thus, the relationship between E_2 and cognition in AD is less than straightforward. It is possible that E_2 may act as a modulating factor in the development of AD, much as diet, family history and gender are factors that can influence the development of heart disease. The finding that the estrogen-using women developed AD an average of three years later than the men and estrogen non-

users supports the notion that estrogen-use may be acting to delay or slow the progress of AD.

The AD patients had the same CRT levels as healthy controls in this study, but higher CRT levels may have been expected on the basis of previous findings of higher CRT levels (Leblhuber et al., 1993; Swaab et al., 1994; Maeda et al., 1990; Davis et al., 1986) and dysregulation of the HPA axis (O'Brien, Ames, Schweitzer, Colman et al., 1996; Hatzinger et al., 1995; Nasman et al., 1995; Nasman et al., 1996; O'Brien, Ames, Schweitzer, Mastwyk et al., 1996) in AD patients compared to controls. Those AD patients who were reported to have elevated CRT levels differed from ours in several ways. They were younger (aged 64.1), with a presenile form of AD (Davis et al., 1986), were more severely demented (MMSE=1.6, Maeda et al., 1991; MMSE=5.2, Leblhuber et al., 1993), were inpatients (Maeda et al., 1991) and were suffering from mixed dementia, not only AD (Maeda et al., 1991). Additionally, all these studies had small sample sizes. However, our findings are consistent with others who failed to find differences in CRT levels between AD patients and controls (Touitou et al., 1982; Dodt et al., 1991; Nasman et al., 1991).

No challenge of the HPA axis was performed in this study, thus HPA dysregulation may have been present but not observed. Severe dysregulation of the HPA axis would likely have been reflected in elevated CRT levels, so it is possible that these Ss, in the early phases of AD, were not suffering from severe HPA dysregulation. However, no comment can be made regarding the presence of subtler forms of HPA dysregulation. It is possible that the elevated CRT levels found in more

severely demented AD patients are a result of prolonged HPA dysregulation, but that such elevations in basal CRT do not occur earlier in the disease progression.

Neither did AD patients have lower DHEAS levels compared with our healthy elderly controls. Although lower levels of DHEAS in AD patients have been reported (Sunderland et al., 1989; Nasman et al., 1991; Yanase et al., 1996), more often than not there have been no differences between AD patients and controls (Leblhuber et al., 1990; 1993; Cuckle et al., 1990; Spath-Schwalbe et al., 1990; Birkenhager-Gillesse et al., 1994). Of the studies that found group differences, the AD patients were either much younger than our sample (61 years, Sunderland et al., 1989) and therefore may have had a familial subtype of AD, or had more severe dementia (Nasman et al., 1990). Our control Ss had similar DHEAS levels to the control Ss in Nasman et al. (1990), but the AD patients in that study had depressed DHEAS levels compared with our AD patients, were far more severely demented (MMSE=2), and were institutionalized. This advanced disease progression may account for the observed decreases in DHEAS, although to date there are no research findings to link dementia severity with depressed DHEAS levels.

The antagonistic effects of DHEAS on GABA in the brain (Majewska, 1995) coupled with its antiglucocorticoid effects (Svec & Lopez-S, 1989), suggest a possible role for DHEAS in the dementia process. The findings of Study 2 that higher DHEAS levels in AD patients were associated with better cognitive performance are interesting, but in the absence of lower levels of DHEAS in patients with AD, an interaction between the dementing process associated with AD and DHEAS in the brain must be

considered. Similar to the proposed actions of E_2, it is possible that DHEAS may act as a modulating factor in the disease progression, working to slow or delay the onset of AD pathology.

If a higher ratio of DHEAS/CRT was beneficial to cognitive performance as others have suggested (Svec & Lopez-S, 1989), the men and estrogen non-users would have shown superior performance compared to the estrogen-users in this study, concomitant with their higher DHEAS/CRT ratios. However, this did not occur in any instance. If any group appeared to have an advantage over the others on the cognitive tests, it was the estrogen-users, particularly the healthy elderly. Thus, in these studies, the measure of the ratio of DHEAS/CRT did not predict cognitive performance in either healthy elderly men and women or in AD patients.

Neuropsychological Tests

Compared to the control Ss, AD patients, predictably, performed worse on every aspect of the RBMT and on the Digit Span tests. The RBMT Total mean score was 2.98 for the AD patients versus 17.59 for the healthy controls. The RBMT was developed for use with head-injured patients and for rehabilitation purposes, and has been shown to accurately reflect everyday memory functioning as determined by its high correlations with objective ratings by a caregiver (Wilson et al., 1989). The administration of three RBMT subtests (Story Recall, Route Recall and Name Recall) to AD patients found that they were very sensitive to gradations of dementia and could distinguish "minimal dementia" from "low-scoring normal" groups (Beardsall & Huppert, 1991). In our study, these same subtests easily discriminated AD patients

mild to moderate dementia from controls.

The most difficult RBMT subtests for the AD patients, as assessed by the magnitude of the group differences between the AD patients and controls, were those that involved recall without a recognition component, such as having to remember a belonging at the end of the test session, or recall a story or a route. These types of tasks are typically those that are most impaired during normal aging (Craik, 1991; 1994), and most hippocampally dependent (Squire, 1992). Those tests that register the least impairment, Digit Spans, are not primarily dependant on the medial temporal lobe memory system (Moscovitch & Winocur, 1992; Kolb & Wishaw, 1985), the area most damaged in AD pathology (West et al., 1994). The functions that Digit Span requires, attention / concentration and short-term memory, are relatively unaffected by increasing age in the normal population (Craik & Jennings, 1992). Neither were the AD patients as impaired on Picture and Face Recognition as they were on the explicit recall tasks. These recognition tasks are also generally easier (Wilson, 1989) and show less impairment with normal aging (Craik, 1991) than do explicit recall tasks. Thus, the AD patients in this sample showed the largest impairments on tasks that depend upon the hippocampal memory system and normally show declining performance with aging (e.g. explicit verbal memory). The fewest impairments in the AD patients occurred on tasks that are not as highly hippocampally dependent (e.g. Digit Span) and tend not to show performance declines with normal aging. It seems, then, that the same patterns of cognitive decline occur in AD patients as in normal elderly subjects, but to a much greater degree.

Supportive evidence comes from a recent study which used MRI scans to investigate the volume of hippocampal and parahippocampal structures and the rate of change in the volume of these structures over several years in very old cognitively healthy Ss compared to Ss who were healthy at the outset but later became demented (Kaye et al., 1997). The Ss who later became demented (pre-demented) had lower hippocampal volumes and lower MMSE scores at the start of the study, although both groups were cognitively healthy and living independently at that time. Both the non-demented and the pre-demented groups showed similar slopes of decreasing hippocampal volume over three to four years. However, the rate of overall temporal lobe volume decrease was greater in the pre-demented population, suggesting that a combination of earlier hippocampal atrophy and a faster rate of loss in the remainder of the temporal lobe is characteristic of those who develop dementia. Thus, there is a constant rate of hippocampal and parahippocampal volume loss with aging regardless of whether one goes on to develop dementia. The decrease in hippocampal volume is consistent with declines in hippocampally dependent cognitive abilities associated with aging (Craik, 1994), although it appears that this process begins at a younger age in demented individuals.

Interestingly, estrogen-use was *not* an exclusion criteria in the Kaye et al. (1997) MRI study, and, unfortunately, the number of Ss in each group who actually took estrogen is not reported. It would be interesting to know whether there were more estrogen-users in the non-demented sample compared to the pre-demented sample in these very elderly Ss, since recent epidemiological studies have shown a lower

incidence of AD in estrogen-using women (Kawas et al., 1987; Tang et al, 1996). Estrogen administration may also slow the death of hippocampal neurons, which occurs with dementia (West et al., 1994). After hippocampal lesioning in female rats, sprouting was decreased in OVX rats compared to intact females, but was restored to intact levels by subsequent administration of estrogen (Scheff et al., 1988a). Also, hippocampal cells exposed *in vitro* to beta-E_2 showed a twofold increase in dendritic spine density (Murphy & Segal, 1996). Thus, it appears that estrogen may act on damaged neurons to restore previous levels of dendritic connectivity. If this is the case in humans as well as rats, it implies that E_2 may be useful in retarding cognitive deterioration in individuals with AD.

Mood Scores

The nature of the mood disturbance in AD patients merits comment. A factor analysis of the GDS items formed several clusters of items, of which the three strongest represented dysphoric mood, positive outlook and mental dullness. That our patients with mild to moderate AD endorsed more of the mental dullness items is likely due to some degree of insight that is often present in the earlier stages of the illness. It was also not surprising that they felt more depressed due to their awareness that this disease is debilitating and chronic.

What was somewhat surprising was that the AD patients were not more likely to endorse a negative outlook towards life. Indeed, they were just as likely as the healthy elderly controls to express basic satisfaction with their life, hopefulness about the future, enjoyment with getting up in the morning and interest in social gatherings.

They did not endorse items relating to feeling that their situation is hopeless, being bothered by thoughts they can't get out of their head, getting restless and fidgety, worrying about the future, worrying about the past, or getting upset over little things. The mean GDS score of the AD patients, in fact, was below the cutoff score for depression of 10, and similar to the mean score of 7.49 in a group of 43 non-depressed but demented men and women (Yesavage, 1986). Thus, although the AD patients were aware of their diminishing mental capacities, and were reacting to it with dysphoric feelings, overall they were not clinically depressed.

Sample Characteristics

Although the healthy elderly control Ss were chosen on the basis of their education and age, it was impossible to match them to the patients with AD on years of education, particularly the men. By selecting Ss from Study 1 who had the fewest years of education, it was possible to create groups of women who were matched with the AD patients, but the control men were still of higher educational status. The difficulty in finding matched, elderly, healthy controls supports the notion that AD is more likely to strike those of lower educational status (Keefover, 1996). Adding to that, our healthy control Ss were volunteers from the community who answered a newspaper advertisement, which may have introduced further bias with respect to their higher level of education. Fifty years ago, it was uncommon for women to pursue higher education at all, so that it is not surprising that the healthy older men were of a higher educational status than the AD men, but the same was not true of the women who had a more restricted educational range.

The mechanism by which higher education offers greater protection against AD is unknown at present. However, rats raised in an enriched environment have larger neurons and more dendrites and synapses in the hippocampus than rats raised in relative isolation (Juraska, 1991). This is particularly the case for female rats, where the hippocampus shows greater plasticity in response to environmental stimuli (Juraska, Fitch, Henderson, & Rivers, 1985). In the degenerative process of AD, hippocampal neuron loss is associated with the severity of AD symptoms, and those who develop AD have smaller hippocampi prior to AD onset (Kaye et al., 1997). Thus, those individuals with a higher level of hippocampal complexity prior to the onset of neural degeneration may experience a slower rate of cognitive deterioration when they develop AD. If it is the case in humans as well as animals that greater environmental enrichment leads to a more complex and highly developed hippocampus, then those individuals with higher education, which could be considered the human equivalent of an enriched environment, may also be protected for longer against AD symptoms. Thus, in this cohort, men would be more protected than women due to their usual higher level of education. It is tempting to speculate that this may, in part, contribute to the greater incidence of AD in women than in men at the present time.

If the human female hippocampus is more plastic in response to environmental enrichment than the male, as it is in the rat (Juraska et al., 1985), women who have higher levels of education may benefit from it more than their male counterparts. It will be interesting to observe any changes in the demographics of AD as the educational level of the women in each aging cohort increases. We will have an

opportunity to test this hypothesis in the next ten or twenty years, when more highly educated women reach the age where the incidence of AD begins to increase.

Summary

Although the AD patients had levels of steroid hormones that did not differ from the healthy elderly controls, they were in the early stages of the disease, and it may be that lowered levels of DHEAS and elevated levels of CRT do not appear until dementia is more severe. The pattern of everyday memory functioning in AD patients mirrored the usual pattern of loss observed in normal aging, but with much greater degrees of impairment. The AD patients were most impaired on explicit recall tasks, followed by recognition tasks then short-term memory and attention tasks. They showed more dysphoric mood and mental dullness symptoms than the healthy controls on the GDS, but were not more likely to have a negative outlook on life. These dysphoric symptoms could indicate a temporary fluctuation in mood brought about by the diagnosis of AD, since many of the Ss in this study had been recently diagnosed. As well, the differing levels of education between AD patients and controls, particularly in the men, suggest a possible protective role of higher education with respect to AD onset.

in the literature. Although progestins did not grossly affect cognition in the small sample of three women on combined estrogen and progestin therapy in Study 1, it is theoretically possible that there may be some effect of progestins on some areas of cognition. Progesterone dampens the growth induced by E_2 in the hippocampus (Murphy & Segal, 1996), and may influence memory via this action. Progestins, however, are needed to protect the uterus from hyperplasia that may result from treatment with E_2 alone. The majority of women have a uterus and need to take a progestin in combination with E_2. Thus, it is important to investigate the possible cognitive consequences of this type of regimen, as no information is currently available.

The analysis of the depressive symptoms in the AD patients illuminated an aspect of the illness that has not received much attention. These mild to moderately demented men and women felt more dysphoric mood than age-matched healthy controls, and they acknowledged having memory and thinking problems. This suggests that individuals in the early stages of AD often retain insight not usually present in more severely demented individuals.

A limitation of this dissertation lies in the uncontrolled nature and naturalistic design of these studies. Without experimentally manipulating independent variables it is impossible to draw any firm conclusions regarding causality. Correlations between hormone levels and memory demonstrate relationships that exist between variables, but do not allow one to conclude that, for example, higher levels of a hormone *cause* enhanced memory performance. Similarly, comparing self-selected

groups of estrogen-users and non-users introduces bias, some of which can be anticipated and controlled statistically, such as educational level. However, there is always the risk that some other, unforeseen variable, may be causing any group differences that are found. Only through random assignment can these problems be avoided. Even though the conclusions derived from these studies are of necessity cautious, the results support previous research and expand the knowledge-base in some relatively unknown areas of this field.

Large, multi-center, double-blind, longitudinal clinical trials with random assignment of Ss to groups are necessary to determine the efficacy of E_2 and/or DHEAS treatment for AD patients, and the direction of causality between AD and hormone replacement therapy. In that context, the type and dosage of hormones administered could be controlled, and Ss could be carefully matched on demographic variables, level of education, and SES. Much also remains to be learned about the neurobiological effects of steroid hormones in the brain. Advanced technologies such as PET and functional MRI are now helping to elucidate the pathology of AD, and have potential for demonstrating hormonal effects on brain chemistry and possibly even on brain morphology. However, new findings with respect to the mechanisms of action of steroid hormones in the brain are likely to come from animal research. It is likely that full understanding of the underlying mechanisms of steroid hormone effects in AD will occur as a result of convergent behavioural and brain imaging studies in humans and through the use of animal models of aging and AD. Then, therapeutic interventions that delay the onset or retard the deterioration of this

devastating disease will hopefully become available.

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Appendix A

Study 1:

Phone Screening Questionnaire
Consent Forms
Background Questionnaire

Assigned I.D.#: _____

PHONE SCREENING PROTOCOL

NAME:_____ AGE:____ DAY: MONTH: YEAR:____ GENDER: male / female

TELEPHONE NO.:_____ (ADDRESS:_____)

The study we are conducting involves a comparison of men's and women's mood states and thinking ability. You will be given several different tests that involve words, drawings, and numbers - as well as a number of questionnaires that ask how you've been feeling over the past little while. Then, at the end of the session, you will be asked to provide a small sample of saliva. The whole session takes about one-and-a-half hours and you will be paid fifteen dollars for your time. Questions?

Is English your first language? yes / no.....(EXC. if did not start very young & use regularly)
If not, when did you begin speaking English?_____
&, how much/often do you speak English?_____

Have you been in any studies in the past? yes / no.....(EXC. if had cognitive testing in the past 5 years)
If so, where was it (were they) conducted?_____
& what did it (they) involve?_____

Have you had any head injuries in the past? yes / no..... (EXC. if very recent or involved unconsciousness)
If so, what type?_____
when did it occur?_____
did it involve a period of unconsciousness?_____

What illnesses do you have or have you been diagnosed with?_____
_____(EXC. major/chronic, e.g., cancer)
Do you have diabetes? yes / no.....(EXC. if yes)
Have you ever had a stroke? yes / no.....(EXC. if yes)
or, a heart attack? yes / no - please describe the details._____

Are you seeing a counsellor, therapist, psychologist, or psychiatrist right now? yes / no
Have you in the past?_____
If yes, what for?_____(EXC. major psychiatric disorder, e.g., major depression)
What sort of treatment have you received?_____(EXC. antidepressants)

What types of medication do you take?_____
_____

ACCEPTED & SCHEDULED FOR: DATE:_____ TIME:_____ LOCATION:_____

NOT ACCEPTED: REASON:_____

_____

IF FEMALE

Are you taking Estrogen Replacement Therapy? yes / no
If so, what type?_____
dosage times?_____
**Please bring in your Estrogen pills with you to the lab, and take one in the morning of the test day (as usual, or, instead of the night before).

_____

**If you wear glasses, or need them to read, please bring them to the laboratory.

CONSENT FORM

We are interested in investigating thinking and mood in healthy men and women over the age of 65. The reason for doing this is to look at what types of changes occur in these areas as people age.

Your participation in this study will involve one visit to our research laboratory, where you will be given a variety of paper and pencil tests which will take about one and a half to two hours to complete. We will also take a small sample of your blood. The reason for this will be explained at the end of the session.

In return for your participation we will pay you $15.00. We will also be happy to share the results of the study with you when it is completed.

We would like to assure you that you are free to withdraw from this study at any time during the test session. As well, all information in this study will be kept strictly confidential. You will be given a subject number and only that number will be attached to any and all personal information or test sheets.

Please sign here to indicate that you have read the above statement and wish to continue in the study at this point.

Signature:_____

Date:_____

Dr. Barbara B. Sherwin	398-6087
Linda E. Carlson	398-6145
Michelle M. Prostak	398-6145

CONSENT FORM

We are interested in investigating thinking and mood in healthy men and women over the age of 65. The reason for doing this is to look at what types of changes occur in these areas as people age.

Your participation in this study will involve one visit to our research laboratory, where you will be given a variety of paper and pencil tests which will take about one and a half to two hours to complete. We will also take a small sample of your blood. The reason for this will be explained at the end of the session.

In return for your participation we will pay you $20.00. We will also be happy to share the results of the study with you when it is completed.

We would like to assure you that you are free to withdraw from this study at any time during the test session. As well, all information in this study will be kept strictly confidential. You will be given a subject number and only that number will be attached to any and all personal information or test sheets.

Please sign here to indicate that you have read the above statement and wish to continue in the study at this point.

Signature:_____

Date:_____

Dr. Barbara B. Sherwin 398-6087
Linda E. Carlson 398-6145

McGill

Department of Psychology

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Montreal, QC, Canada H3A 1B1

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Fax: (514) 398-4896

I _____ grant permission to Dr. Barbara B. Sherwin to contact my physician, Dr. _____ at _____ clinic / hospital, in order to confirm information regarding:

___ medication / hormone dosages.

___ details of my _____ surgery.

___ other: _____.

_____ _____

Date Signature

Healthy Elderly Study

Subject # _____
Date _____
Examiner _____

PERSONAL INFORMATION FORM

GENERAL

Age:_____ DOB: D____ M____Y____ Gender: M / F

Marital status: M S W (When ____) D (When _____)
If D or W: How well did you handle the divorce/death?

children, grandchildren
+ Where living
Recent relocation / estrangement?

First language: Other languages:

Ethnic origin:

How long have you lived in Montreal? Where lived before?

EDUCATION + SES

FORMAL EDUCATION: Years of school Degree obtained

Informal Education: (eg, night school, etc)

Hobbies or pastimes:

Occupation:_____
SES Blishen_____ SES Pineo and Porter_____
Spouses's occupation:_____
SES Blishen_____ SES Pineo and Porter_____

Has your standard of living changed very much recently / since retirement / death, etc?

PSYCHIATRIC HISTORY

Have you had any recent, major stressful experiences?

Any treatment? yes / no
If yes, what for (diagnosis)?

Treatment? (meds, length, "talking", etc + when occurred)

NEUROLOGIC HISTORY

Head injury?	yes / no. If yes, when
Loss of consciousness	yes / no. If yes, when
Seizures?	yes / no. If yes, when
Severe, recurrent headaches?	yes / no. If yes, when
Stroke?	yes / no. If yes, when
Car accident, fall down?	yes / no. If yes, what and when
Other?	yes / no. If yes, what and when

OTHER MEDICAL CONDITIONS

Vascular disorders? yes / no. If yes, when
Heart condition? yes / no. If yes, when
Heart attack? yes / no. If yes, when
High blood pressure? yes / no. If yes, when
Diabetes? yes / no. If yes, when
Other (pain, etc)? yes / no. If yes, what and when

Surgery? yes / no. If yes, what and when

Hospitalizations? yes / no. If yes, why and when

MENSTRUAL HISTORY

Age at menopause?
(Time since menopause)
Remarkable, memorable symptoms?

Any estrogen treatment? yes / no.

If current, PILLS: the dosage_____ and the day of cycle _____

Progestin use? Type and dosage:
What time taken today?

INJECTION: day since last injection _____

When (what year, how many years ago) did treatment begin?

If not current, type used, dosage if known (ask color of the pills)

Progestin use? Type and dosage:

When (what year, how many years ago) did treatment begin and end?

Ovaries intact? yes / no. If not, when removed?

Uterus intact? yes / no. If not, when removed?

ALCOHOL AND DRUG USE

Alcohol: current use: none / occasional / moderate (<2/day) / heavy (>2/day) / problem
Past problem: yes / no. If yes, when

Coffee drinker? yes / no. If yes, how much a day?

Cigarette smoker? yes / no. If yes, how much a day?

Past 24 hours? How much: coffee ___ cups
cigarettes ___ cigarettes
alcohol ___ drinks

OTHER MEDICATIONS: Types and dosages:

MISCELLANEOUS INFORMATION:

Appendix B

Study 1:

Traditional Memory Test Forms
Times 1 and 2

: going to read you a little story which is just a few lines long.
:ten carefully and try to remember it just the way I say it - As close to the same words as you can remember.
hen I m through, I want you to tell me everything I read to you. You should tell me as you can remember, even if you're not sure (of it).
a you ready? Okay.

Healthy Elderly Study

Testing ended at:_____

Subject # _____
Date _____
Examiner _____

Immediate Paragraph recall — Set I

Anna Thompson / of South / Boston, / employed / as a scrub woman / in an office building, / reported / at the city hall / station / that she had been held up / on State Street / the night before / and robbed / of fifteen dollars. / She had four / little children, / the rent / was due, / and they had not eaten / for two days. / The officers, / touched by the woman's story, / made up a purse / for her.

Total:_____

Now, what did I read to you? - Tell me everything and begin at the beginning.

Now I'm going to read you another little story. See how much of this one you can remember.
As with the first story, try to remember it just the way I say it. Ready? Okay. -

The American / liner / *New York* / struck a mine / near Liverpool / Monday / evening. / In spite of a blinding / snowstorm / and darkness, / the sixty / passengers including 18 / women, / were all rescued, / though the boats / were tossed about / like corks / in the heavy sea. / They were brought into port / the next day / by a British / steamer.

Total:_____

1 + 2 = _____

Now, what did I read to you? - Tell me everything and begin at the beginning.

ALLOW AT LEAST 10 SEC. TO ELAPSE BEFORE STARTING THE NEXT SUBTEST

Listen carefully, because after I'm through I'm going to ask you which words were together.
For example, if the words were EAST - WEST / GOLD - WALK, then - when I say the word EAST, you would answer (PAUSE)... WEST.
And when I say the word GOLD, you would answer (PAUSE)... WALK.
(You can see that some of the words will sound as though they go together, like EAST - WEST, while others won't, like GOLD - WALK. Okay?)
So, do you understand the instructions? Now, listen carefully as I read the list:
READ WORDS 1 SEC. APART WITH 2 SEC. BETWEEN PAIRS. RESPOND - 'That's right' or 'No, the word is _____.'
PAUSE 5 SEC. BEFORE RECALL. PAUSE 5 SEC. BETWEEN SETS. THEN SAY, 'Now, we'll try it again. Listen.' OR 'Listen again.'

Time testing ended _____
Subject # _____
Date _____
Examiner _____

Immediate Paired Associates

First Presentation	
Metal	- Iron
Baby	- Cries
Crush	- Dark
North	- South
School	- Grocery
Rose	- Flower
Up	- Down
Obey	- Inch
Fruit	- Apple
Cabbage	- Pen

Second Presentation	
Rose	- Flower
Obey	- Inch
North	- South
Cabbage	- Pen
Up	- Down
Fruit	- Apple
School	- Grocery
Metal	- Iron
Crush	- Dark
Baby	- Cries

Third Presentation	
Baby	- Cries
Obey	- Inch
North	- South
School	- Grocery
Rose	- Flower
Cabbage	- Pen
Up	- Down
Fruit	- Apple
Crush	- Dark
Metal	- Iron

1. north	**south**	1. cabbage	pen	1. obey	inch
2. fruit	**apple**	2. baby	**cries**	2. fruit	**apple**
3. obey	inch	3. metal	**iron**	3. baby	**cries**
4. rose	**flower**	4. school	grocery	4. metal	**iron**
5. baby	**cries**	5. up	**down**	5. crush	dark
6. up	**down**	6. rose	**flower**	6. school	grocery
7. cabbage	pen	7.obey	inch	7. rose	**flower**
8. metal	**iron**	8. fruit	**apple**	8. north	**south**
9. school	grocery	9. crush	dark	9. cabbage	pen
10. crush	dark	10. north	**south**	10. up	**down**

Score: **Easy**	____	**Easy**	_____
Hard ___ x2	_____	Hard ____ x2	_____
Subtotals:	_____	_____	_____

Total score: _____

ATERIALS: LITTLE SPIRAL & FOLDERS A & B
n going to show you some figures - each one paired with a different color.
s you look at the figures, try to remember the color that goes with each figure.
ter I've shown you the figures with their colors, I'll show you the figures alone -
nd for each figure I'll ask you to point to the color that went with it, in this folder (PLACE FOLDER A IN FRONT OF S. - UNOPENED)

gA - Here's an example of what I'll ask you to do. (PRESENT SPIRAL - OPEN TO 1ST DEMONSTRATION CARD)
his figure here (POINT) goes with this color (POINT) - TURN PAGE. And this figure (POINT) goes with this color - TURN PAGE
ow look at this figure, it has no color square with it - Try to remember what color goes with it.
(FOLDER A) - Look at these colors and point to the one that goes with this figure (ALLOW 3 SEC. - PROMPT "If you don't remember, just
RESPONSE "Yes. / That's right." OR "No, it was this one / No, this is the right color."
(ALSO - "You don't have to name the color - just point to it here.")
gB - (TURN PAGE) - Which color goes with this figure? RESPONSE

hat was an example of what I want you to do. (REMOVE FOLDER A AND REPLACE IT WITH FOLDER B, UNOPENED)
ow I'll show you some new figures paired with different colors (OPEN FOLDER B)
ere are the colors. Can you tell them all apart? Do any of them look the same to you? (NOTE ANY DIFFICULTY)
ow I will show you six new figures, each one paired with one of these colors (POINT TO FOLDER B). You'll see each pair for just 3 seconds.
fter presenting all 6 cards, I'll show you the same figures, one at a time, but in a different order and without the colors.
hen I'll ask you to point to the color in this folder (POINT) that goes with each figure - just as you did in the samples. Are you ready? Okay.

1 - (CLOSE FOLDER B) (EXPOSE CARDS - 1 PAIR EVERY 3 SEC.) 'Look at this pair.'

ow I will show you the figures without the colors. As you look at each figure, point to the color in this folder (POINT) that goes with it.
you are not sure, make a guess. (OPEN FOLDER B)
how me what color goes with this figure - point to it on this card. (ALLOW INTERVAL OF AT LEAST 5 SEC.) RESPONSE

2 - (CLOSE FOLDER B) Now let's try it once more. Here are the same figures paired with the same colors, only now in a different order.
EXPOSE CARDS - 1 PAIR EVERY 3 SEC.)
OPEN FOLDER B) Now I will show you the figures without their colors.
Look at each figure and point to the color that goes with it, here in this folder. (POINT) RESPONSE

3 Now let's try it another time.

4 - #6 REPEAT INSTRUCTIONS

DISCONTINUE WHEN ALL 6 CORRECT ON THIRD OR SUBSEQUENT PRESENTATION

VISUAL PAIRED ASSOCIATES I

If the examinee answers all six items correctly on Set III, discontinue the subtest. Otherwise, present Sets IV, V, and VI until all six items are correct.

SET I				SET II				SET III			
Item	Key	Response	Score 1 or 0	Item	Key	Response	Score 1 or 0	Item	Key	Response	Score 1 or 0
1	G			1	Y			1	B		
2	Pu			2	R			2	G		
3	R			3	B			3	Pu		
4	Y			4	Pu			4	Pk		
5	Pk			5	G			5	Y		
6	B			6	Pk			6	R		
		Set I Total				Set II Total				Set III Total	
										Max. = 18 Total Sets I-III	

SET IV				SET V				SET VI			
Item	Key	Response	Score 1 or 0	Item	Key	Response	Score 1 or 0	Item	Key	Response	Score 1 or 0
1	G			1	Pu			1	G		
2	Pu			2	B			2	Y		
3	R			3	Y			3	B		
4	Y			4	Pk			4	R		
5	Pk			5	R			5	Pu		
6	B			6	G			6	Pk		
		Set IV Total				Set V Total				Set VI Total	

MATERIALS: BIG SPIRAL AND STOPWATCH

#1 (OPEN FRONT COVER OF BIG SPIRAL) When I turn this page you will see a design. I will show it to you for 5 seconds. After that I will show you a second page with three designs that include the first design. You should remember the first design, because I will ask you to point it out on the page with three designs. Do you understand? Okay.

#1 (TURN FIRST PAGE) Look at this design and try to remember it. (5 SEC. - TURN PAGE) Look at the 3 designs here. Point to the one that is the same as the one you just saw. (PROMPT AFTER 5 SEC.) Which one is it? (RECORD RESPONSE) (PAUSE 5 SEC.)

(IF NO RESPONSE OR INCORRECT) FLIP BACK TO BEGINNING - Let's try that one again. Look at this design and try to remember it. (5 SEC.) (TURN PAGE) Look at these three designs and point to the one that you just saw.

#2 Now I will show you a page with three designs. After 15 seconds I will show you another page with 3 designs that include the 3 on the first page. Then I will ask you to point out the three designs from the first page. Do you understand? (TURN PAGE) Look at these designs carefully, and try to remember them. (15 SEC. - TURN PAGE) Look at these designs and point to the 3 you just saw. (PROMPT AFTER 10 SEC.) Can you point to the designs you just saw? (30 SEC.) (TURN TO BLANK PAGE - PAUSE 5 SEC.)

#3 Here are three more designs. Look at them carefully and try to remember them. (15 SEC. - TURN PAGE) Look at these designs and point to the three that you just saw. (ALLOW 30 SEC. - TURN TO BLANK PAGE - PAUSE 5 SEC.)

#4 (SAME AS #3)

FIGURAL MEMORY Administer all items.			
Item	Key	Response	Score 1 or 0
1	1		
2	3, 5, 8	Score 3, 2, 1, or 0	
3	1, 6, 7		
4	2, 4, 9		
		Max. = 10 Total	

PLACE FOLDED PAPER AND APPROPRIATE CARD, FACE DOWN, IN FRONT OF S.)
m going to show you some drawings, one at a time, which I will want you to copy here on this sheet (POINT)
ou will have just 10 seconds to look at each drawing. Then, I will take it away and let you draw it from memory.
)o not begin to draw it until I say "go". - Ready? - Okay. (TURN CARD FACE UP)
.ook at it carefully. (10 SEC. - REMOVE)
low draw it in this space - Go. (REPEAT FOR CARDS B AND C)

PROMPTS - Don't worry about your artistic ability, just draw it as best you can. OR, Just draw your best guess.

VISUAL REPRODUCTION SCORING SUMMARY (see Appendix B in Manual for Scoring Criteria).

	VR I	VR II
CARD A		
Staffs:		
1. Unbroken/straight/equal		
2. Intersect at midpoints		
3. Cross at right angles		
4. Not rotated (15 degrees)		
Flags:		
5. Correct direction		
6. Share side with staff		
7. Square in shape		
TOTAL		
CARD B		
Circles:		
1. Large circle		
2. Medium circle inside large circle		
3. Small circle inside medium circle		
4. Large circle and medium circle touch (top)		
5. Small circle and medium circle touch (bottom)		
6. Round/closed		
7. Correct proportion		
TOTAL		
CARD C		
Large Square:		
1. Square in shape		
2. Vertical & horizontal lines		
3. Not rotated (15 degrees)		
4. Each quadrant has 4 dots		
Medium Squares:		
5. In 4 quadrants not touching		
6. Square in shape		
7. Vertical & horizontal lines		
8. None rotated (15 degrees)		
9. Equal size/proportion		
TOTAL		

	VR I	VR II
CARD D		
Rectangles:		
1. Do not touch/intersect		
2. Interior angles 90 degrees		
3. Not rotated (15 degrees)		
4. 2 small to right of large		
5. Uppermost is taller		
6. Bases of large and small level		
7. Top of large higher than small		
8. Bases of 3 equally long		
9. Height of large > width		
10. Heights of small < width		
Circle Segment:		
11. Figure to right of rectangles		
12. Arc curves to right		
13. Symmetry/proportion		
14. Not rotated (15 degrees)		
Triangle:		
15. Figure to right of segment		
16. Vertex touches midpoint		
17. Contains 90 degree angle		
18. Not rotated (15 degrees)		
TOTAL		
Total (Cards A through D) Max. = 41		

Notes:

BEFORE CARD D - This next one is a little harder because it has two drawings on it. I want you to look at both of them carefully. Again you will have just 10 seconds to look at the card. Then I will take it away and you will make both drawings from memory. Make the drawing on the left side of the card here. (POINT) Make the drawing on the right side of the card here (POINT). - Ready? (TURN OVER-10 SEC.) (REMOVE) Now go ahead and make the two drawings.

ALLOW AT LEAST 10 SEC. TO ELAPSE BEFORE BEGINNING THE NEXT SUBTEST.

FORWARD - I am going to say a group of numbers. Listen carefully, and when I'm through, say them right after me. (READ 1 DIGIT PER SEC.)

DIGIT SPAN Discontinue after failure on both trials of any item.
Administer both trials of each item, even if the first trial is passed.

DIGITS FORWARD					Score
Item	Trial I	Pass-Fail	Trial II	Pass-Fail	2, 1, or 0
1.	6-2-9		3-7-5		
2.	5-4-1-7		8-3-9-6		
3.	3-6-9-2-5		6-9-4-7-1		
4.	9-1-8-4-2-7		6-3-5-4-8-2		
5.	1-2-8-5-3-4-6		2-8-1-4-9-7-5		
6.	3-8-2-9-5-1-7-4		5-9-1-8-2-6-4-7		
				Max. = 12	

BACKWARD - Now I'm going to say some more numbers, but this time when I finish each group I want you to say them backwards.
For example, if I say 2-4-3, what would you say? RESPOND - "that's right"
(OR, IF INCORRECT - "No, I said 2-4-3, so to say them backwards you would need to say 3-4-2.
Now try these numbers. Remember, you are to say them backwards. Ready? 1-6-8.) (GIVE NO SUBSEQUENT HELP)

Item	Trial I	Pass-Fail	Trial II	Pass-Fail	2, 1, or 0	
1.	5-1		3-8			
2.	4-9-3		5-2-6			
3.	3-8-1-4		1-7-9-5			
4.	6-2-9-7-2		4-8-5-2-7			
5.	7-1-5-2-8-6		8-3-1-9-6-4			
6.	4-7-3-9-1-2-8		8-1-2-9-3-6-5			
				Max. = 12 Total Backward		Max. Total = 24

VISUAL MEMORY SPAN (MATERIALS: BLOCK CARDS) FORWARD - (PRESENT CARD 1, RED BLOCKS, FACE DOWN)
(POINT TOWARDS CARD) On the other side of this card are a number of red squares.
When I turn the card face up, I will touch some of the squares, one after another.
Watch carefully as I do it, because as soon as I'm through, I'll ask you to touch the same squares as I did - in the same order.
(TURN CARD 1 OVER) 1A. Watch me. (TOUCH ONE SQUARE PER SEC.) (PAUSE 2 SEC. AND SAY:) Now you do it. Touch the same squares I did in the same order.
1B. Now we'll do another one. First watch me, then you touch the same squares I do in the same order.
2A. Let's try one that's a little harder. (REPEAT IN SAME MANNER)

Item	Trial I	Pass-Fail	Trial II	Pass-Fail	2, 1, or 0
1.	2-6		8-4		
2.	2-7-5		8-1-6		
3.	3-2-8-4		2-6-1-5		
4.	5-3-4-6-1		3-5-1-7-2		
5.	1-7-2-8-5-4		7-3-6-1-4-8		
6.	8-2-5-3-4-1-6		4-2-6-8-3-7-5		
7.	7-5-6-3-8-7-4-2		1-6-7-4-2-8-5-3		
				Max. = 14 Total Forward	

TAPPING BACKWARD Administer Tapping Backward even if examinee scores 0 on Tapping Forward.					Score
Item	Trial I	Pass-Fail	Trial II	Pass-Fail	2, 1, or 0
1.	3-6		7-4		
2.	6-8-5		3-1-8		
3.	8-4-1-6		5-2-4-1		
4.	4-6-8-5-2		8-1-6-3-7		
5.	7-1-8-3-6-2		3-8-1-7-5-4		
6.	1-5-2-7-4-3-8		6-7-4-3-1-5-2		
				Max. = 12	Max. Total = 26

BACKWARD - (PRESENT CARD 2, GREEN BLOCKS, FACE DOWN)
This card contains a number of squares like those on the card we just [illegible] except that the squares are green.
In this test I'm going to touch the squares one at a time as I did before.
But this time when I'm through I want you to touch the squares in reverse order.
(TURN CARD 2 OVER) 1A. Watch me. (TAP 2-7). Now you do it. Touch the same squares that I did but in reverse order. (RESPOND) That's right.
(IF NOT BACKWARD) Remember, on this part of the test you have to repeat them backwards.
(IF STILL WRONG) No, I touched this square first (TAP SQUARE 2) and then this square (TAP SQUARE 7). You are to touch them backwards,
like this (TAP 7 THEN 2). (GIVE 2ND PRACTICE TRIAL - TAP 8-1.) Now, you touch them in reverse order.

Do you remember the little stories I read to you a while ago? Now I want you to tell me the stories again. Tell me everything and begin at the beginning.

Healthy Elderly Study

Tested at:_____ Subjectt # _____
Delay: Date _____
Examiner _____

Delayed Paragraph recall -- Set I

Anna Thompson / of South / Boston, / employed / as a scrub woman / in an office building, / reported / at the city hall / station / that she had been held up / on State Street / the night before / and robbed / of fifteen dollars. / She had four / little children, / the rent / was due, / and they had not eaten / for two days. / The officers, / touched by the woman's story, / made up a purse / for her.

Total:_____

The American / liner /*New York* / struck a mine / near Liverpool / Monday / evening. / In spite of a blinding / snowstorm / and darkness, / the sixty / passengers including 18 / women, / were all rescued, / though the boats / were tossed about / like corks / in the heavy sea. / They were brought into port / the next day / by a British / steamer.

Total :_____

1 +-2 = _____

while ago I read you a list of words, 2 at a time. Then I read you the first word in each pair, and you were to tell me the word that went with it.
or example, if the words were EAST - WEST, and I said the word EAST you would answer (PAUSE) WEST. Do you remember? (PAUSE)
ow I want to see how well you remember the word pairs. I'm going to read you one of the words, and you are to tell me the word that goes with it.
he first word is OBEY. What word went with it? (ALLOW A MAX OF 10 SEC. THEN CONTINUE - DO NOT CORRECT)

Healthy Elderly Study

Time tested: _____
Delay:

Subject # _____
Date _____
Examiner _____

Paired Associates

1. obey inch
2. fruit **apple**
3. baby **cries**
4. metal **iron**
5. crush dark
6. school grocery
7. rose **flower**
8. north **south**
9. cabbage pen
10. up **down**

Score: **Easy** ____

Hard ____ x2 _____

Total score: _____

MATERIALS: SMALL SPIRAL AND FOLDER B
A little while ago I showed you some figures, each one paired with a different color. (PLACE FOLDER B OPENED IN FRONT OF S.) These were the colors,
Now I'm going to show you the figures again, and you try to remember which color went with each one.
(PUT SMALL SPIRAL IN FRONT OF S. AND OPEN TO LAST DIVIDER - SUBTEST 10) (TURN OVER 1ST CARD)
Here is the first figure. Look at these colors (POINT TO FOLDER B) and point to the one that goes with this figure (ALLOW 10 SEC. - DO NOT CORRECT)
(TURN PAGE) Which color goes with this figure? Point to it.
(REPEAT INSTRUCTIONS FOR ALL 6 CARDS - DO NOT CORRECT)

VISUAL PAIRED ASSOCIATES II			
Item	Key	Response	Score 1 or 0
1	Pk		
2	R		
3	G		
4	B		
5	Y		
6	Pu		
		Max. = 6 Total	

TERIALS: SELECTIVE REMINDING CARDS AND STOPWATCH
going to show you some words written on these cards.
ould like you to look at each card, read the word out loud, and study the word until I take the card away.
ar you have seen and read all of the cards, I will ask you to tell me as many words as you can remember seeing and reading.
hat point, I will remind you of any words you did not remember.
will be doing this test a number of times, so you will have plenty of chances to learn the words. Any questions?
HOW EACH CARD FOR 5 SEC. - CORRECT MISPRONUNCIATIONS.)
ow I would like you to tell me all of the words in any order. (AFTER 60 SEC. WITH NO NEW WORDS:)
e [redacted] you did not remember were...
ow I would like you to tell me all the words you can remember, including the ones I did not remind you of, in any order.
ONTINUE FOR 5 TRIALS. ON THE LAST TRIAL, REMIND THE S. OF WORDS NOT GIVEN.)

Subject # _____
Date _____
Examiner _____

Selective Reminding Test : I

Trial:	1	2	3	4	5	6	Total
throw							
lily							
film							
discreet							
loft							
beef							
street							
helmet							
snake							
dug							
pack							
tin							

Intrusions:
(list)

	1	2	3	4	5	6	Totals
# recall							
LTR							
STR							
LTS							
CR							
CLTR							
RLTR							
reminders							
intrusions							
cum. int							

For the next few minutes, I'm going to ask you to list as many things as you can think of that belong to different categories.
(ALLOW 60 SEC. FOR EACH CATEGORY)

Healthy Elderly Study

Patient Identification Number _____

Date _____

Examiner's Initials _____

CATEGORY FLUENCY: 1

First I would like you to list as many animals as you can think of. They can be animals of any kind, that live anywhere - on land, in the water, in the air, on a farm, in the zoo, whatever. Just list as many different animals as you can think of.

Now we will switch to the category clothing. I would like you to list as many pieces of clothing as you can. Men's, women's, children's, indoor, outdoor, whatever. Go ahead.

Now I would like you to list as many kinds of fruit as you can think of. Go ahead.

	ANIMALS	CLOTHING	FRUITS
15"			
30"			
45"			
60"			

	ANIMALS	CLOTHING	FRUITS
Total Output	____	____	____
Total Correct	____	____	____
Perseveration	____		
Non-Words	____	____	____
Other Categories	____	____	____

Healthy Elderly Study

Patient Identification Number _____

Date _____

Examiner's Initials _____

CATEGORY FLUENCY: II

Now I would like you to list as many first names of people as you can. They can be mens or women's names, people you know or don't know. Go ahead.

Now I would like you to list as many kinds of vegetables as you can. Go ahead.

	FIRST NAMES	VEGETABLES
15"		
30"		
45"		
60"		

	FIRST NAMES	VEGETABLES
Total Output	____	____
Total Correct	____	____
Perseveration		
Non-Words	____	____
Other Categories	____	____

tle while ago you read some words on cards, remembered them, and told them to me. I reminded you of the words you forgot.
you remember that test? (PAUSE) Now I would like you to tell me all of the words you can remember from that list.
IF ALL WORDS NOT RECALLED:)
the words you did not remember. I am going to read you 4 words. One of the 4 words was on the list.
ould like you to listen to all four words, & then tell me which one you think was on the list. I would like you to guess if you're not quite sure.

Healthy Elderly Study

Subject # _____
Date _____
Examiner _____

SRT I: Recognition

throw	throw	toss	through	plate
lily	flower	lilt	intent	lily
film	film	movie	slave	kiln
discreet	waver	cautious	discreet	district
loft	soft	loft	attic	tack
beef	beet	meat	clue	beef
street	stream	street	speed	road
helmet	helmet	armor	bacon	velvet
snake	smoke	serpent	snake	pool
dug	hoed	dug	hay	dog
pack	blank	bundle	pack	puck
tin	ton	shirt	foil	tin

____ recall correct. Intrusions:

____ recognition correct.

____ total delayed correct.

going to read you a little story which is just a few lines long.
sten carefully and try to remember it just the way I say it - As close to the same words as you can remember.
hen I'm through, I want you to tell me everything I read to you. You should tell me as you can remember, even if you're not sure (of it).
s you ready? Okay.

Healthy Elderly Study

Testing ended at:_____

Subject # _____
Date _____
Session # ____
Examiner _____

Paragraph recall – Set II

Dogs / are trained / to find / the wounded / in war time. / Police dogs / are also trained/ to rescue / drowning people. / Instead of running / down to the water / and striking out./ they are taught / to make / a flying leap / by which they save / many swimming strokes/ and valuable / seconds of time. / The European / sheep dog / makes the best / police / dog.

Total:_____

Total:_____

Now, what did I read to you? - Tell me everything and begin at the beginning.

Now I'm going to read you another little story. See how much of this one you can remember.
As with the first story, try to remember it just the way I say it. Ready? Okay. -

Many / school / children / in northern / France / were killed / or fatally hurt / and others / seriously injured / when a shell / wrecked / the schoolhouse / in their village. / The children / were thrown / down a hillside / and across / a ravine / a long distance / from the schoolhouse. / Only two / children / escaped uninjured.

Total:_____

1 + 2 = _____

Now, what did I read to you? - Tell me everything and begin at the beginning.

ALLOW AT LEAST 10 SEC. TO ELAPSE BEFORE STARTING THE NEXT SUBTEST

Paired Associates - Version II

Subject no._____

First Trial

Knife	- Sharp
Lead	- Pencil
Jury	- Eagle
Country	- France
In	- Although
Murder	- Crime
Necktie	- Cracker
Lock	- Door
Come	- Go
Dig	- Guilty

Second Trial

Lock	- Door
Dig	- Guilty
Come	- Go
Jury	- Eagle
Knife	- Sharp
Country	- France
In	- Although
Murder	- Crime
Necktie	- Cracker
Lead	- Pencil

Third Trial

Lead	- Pencil
Lock	- Door
Necktie	- Cracker
Come	- Go
Dig	- Guilty
Country	- France
Jury	- Eagle
Knife	- Sharp
In	- Although
Murder	- Crime

First Recall

_____Jury - Eagle
_____In - Although
_____Lock - Door
_____Come - Go
_____Necktie- Cracker
_____Dig - Guilty
_____Knife - Sharp
_____Lead - Pencil
_____Country- France
_____Murder - Crime

Total Hard x 2 _____
Total Easy _____

Total Trial one _____

Second Recall

_____Come - Go
_____Necktie- Cracker
_____Country- France
_____Lead - Pencil
_____Lock - Door
_____Dig - Guilty
_____Jury - Eagle
_____In - Although
_____Murder - Crime
_____Knife - Sharp

Total Hard x 2 _____
Total Easy _____

Total Trial Two _____

Third Recall

_____Lock - Door
_____Come - Go
_____Murder - Crime
_____Jury - Eagle
_____Necktie- Cracker
_____Lead - Pencil
_____Knife - Sharp
_____In - Although
_____Country- France
_____Dig - Guilty

Total Hard x 2 _____
Total Easy _____

Total Trial Three _____

_____Overall Total

IALS: LITTLE SPIRAL & FOLDERS A & B
g to show you some figures - each one paired with a different color.
look at the figures, try to remember the color that goes with each figure.
e shown you the figures with their colors, I'll show you the figures alone -
each figure I'll ask you to point to the color that went with it, in this folder (PLACE FOLDER A IN FRONT OF S. - UNOPENED)

Here's an example of what I'll ask you to do. (PRESENT SPIRAL - OPEN TO 1ST DEMONSTRATION CARD)
ure here (POINT) goes with this color (POINT) - TURN PAGE. And this figure (POINT) goes with this color - TURN PAGE
ok at this figure, it has no color square with it - Try to remember what color goes with it.
FOLDER A) - Look at these colors and point to the one that goes with this figure (ALLOW 3 SEC. - PROMPT "If you don't remember, just
") RESPONSE "Yes, / That's right." OR "No, it was this one / No, this is the right color."
SO - You don't have to name the color - just point to it here.")
- (TURN PAGE) - Which color goes with this figure? RESPONSE

was an example of what I want you to do. (REMOVE FOLDER A AND REPLACE IT WITH FOLDER B. UNOPENED)
ll show you some new figures paired with different colors (OPEN FOLDER B)
are the colors. Can you tell them all apart? Do any of them look the same to you? (NOTE ANY DIFFICULTY)
will show you six new figures, each one paired with one of these colors (POINT TO FOLDER B). You'll see each pair for just 3 seconds.
presenting all 6 cards. I'll show you the same figures, one at a time, but in a different order and without the colors.
'll ask you to point to the color in this folder (POINT) that goes with each figure - just as you did in the samples. Are you ready? Okay.

CLOSE FOLDER B) (EXPOSE CARDS - 1 PAIR EVERY 3 SEC.) "Look at this pair."

will show you the figures without the colors. As you look at each figure, point to the color in this folder (POINT) that goes with it.
are not sure, make a guess. (OPEN FOLDER B)
me what color goes with this figure - point to it on this card. (ALLOW INTERVAL OF AT LEAST 5 SEC.) RESPONSE

CLOSE FOLDER B) Now let's try it once more. Here are the same figures paired with the same colors, only now in a different order.
OSE CARDS - 1 PAIR EVERY 3 SEC.)
EN FOLDER B) Now I will show you the figures without their colors.
at each figure and point to the color that goes with it, here in this folder. (POINT) RESPONSE

ow let's try it another time.

s6 REPEAT INSTRUCTIONS

CONTINUE WHEN ALL 6 CORRECT ON THIRD OR SUBSEQUENT PRESENTATION

VISUAL PAIRED ASSOCIATES I

If the examinee answers all six items correctly on Set III, discontinue the subtest. Otherwise, present Sets IV, V, and VI until all six items are correct.

SET I				SET II				SET III			
Item	Key	Response	Score 1 or 0	Item	Key	Response	Score 1 or 0	Item	Key	Response	Score 1 or 0
1	G			1	Y			1	B		
2	Pu			2	R			2	G		
3	R			3	B			3	Pu		
4	Y			4	Pu			4	Pk		
5	Pk			5	G			5	Y		
6	B			6	Pk			6	R		
		Set I Total				Set II Total				Set III Total	
										Max. = 18 Total Sets I-III	

SET IV				SET V				SET VI			
Item	Key	Response	Score 1 or 0	Item	Key	Response	Score 1 or 0	Item	Key	Response	Score 1 or 0
1	G			1	Pu			1	G		
2	Pu			2	B			2	Y		
3	R			3	Y			3	B		
4	Y			4	Pk			4	R		
5	Pk			5	R			5	Pu		
6	B			6	G			6	Pk		
		Set IV Total				Set V Total				Set VI Total	

TERIALS: BIG SPIRAL AND STOPWATCH

(OPEN FRONT COVER OF BIG SPIRAL) When I turn this page you will see a design. I will show it to you for 6 seconds.
ar that I will show you a second page with three designs that include the first design.
J should remember the first design, because I will ask you to point it out on the page with three designs. Do you understand? Okay.

(TURN FIRST PAGE) Look at this design and try to remember it. (5 SEC. - TURN PAGE)
ok at the 3 designs here. Point to the one that is the same as the one you just saw.
ROMPT AFTER 5 SEC.) Which one is it? (RECORD RESPONSE) (PAUSE 5 SEC.)

(IF NO RESPONSE OR INCORRECT) FLIP BACK TO BEGINNING - Let's try that one again. Look at this design and try to remember it.
SEC.) (TURN PAGE) Look at these three designs and point to the one that you just saw.

Now I will show you a page with three designs. After 15 seconds I will show you another page with 9 designs that include the 3 on the first page.
an I will ask you to point out the three designs from the first page. Do you understand? (TURN PAGE)
ok at these designs carefully, and try to remember them. (15 SEC. - TURN PAGE)
ok at these designs and point to the 3 you just saw. (PROMPT AFTER 10 SEC.) Can you point to the designs you just saw? (30 SEC.)
URN TO BLANK PAGE - PAUSE 5 SEC.)

Here are three more designs. Look at them carefully and try to remember them. (15 SEC. - TURN PAGE)
ok at these designs and point to the three that you just saw. (ALLOW 30 SEC. - TURN TO BLANK PAGE - PAUSE 5 SEC.)

(SAME AS #3)

FIGURAL MEMORY Administer all items.			
Item	Key	Response	Score 1 or 0
1	1		
2	3, 5, 8	Score 3, 2, 1, or 0	
3	1, 6, 7		
4	2, 4, 9		
		Max. = 10 Total	

FOLDED PAPER AND APPROPRIATE CARD, FACE DOWN. IN FRONT OF S.)
to show you some drawings, one at a time, which I will want you to copy here on this sheet (POINT)
have just 10 seconds to look at each drawing. Then, I will take it away and let you draw it from memory.
egin to draw it until I say "go". - Ready? - Okay. (TURN CARD FACE UP)
it carefully. (10 SEC. - REMOVE)
w it in this space - Go. (REPEAT FOR CARDS B AND C)

'S - Don't worry about your artistic ability, just draw it as best you can. OR, Just draw your best guess.

.L REPRODUCTION SCORING SUMMARY (see Appendix B in Manual for Scoring Criteria).

	VR I	VR II
CARD A		
:broken/straight/equal	____	____
:ersect at midpoints	____	____
oss at right angles	____	____
ot rotated (15 degrees)	____	____
orrect direction	____	____
are side with staff	____	____
quare in shape	____	____
TOTAL	____	____
CARD B		
s:		
arge circle	____	____
fedium circle inside large circle	____	____
mall circle inside medium circle	____	____
arge circle and medium circle ouch (top)	____	____
mall circle and medium circle ouch (bottom)	____	____
ound/closed	____	____
Correct proportion	____	____
TOTAL	____	____
CARD C		
e Square:		
Square in shape	____	____
Vertical & horizontal lines	____	____
Not rotated (15 degrees)	____	____
Each quadrant has 4 dots	____	____
ium Squares:		
In 4 quadrants not touching	____	____
Square in shape	____	____
Vertical & horizontal lines	____	____
None rotated (15 degrees)	____	____
l size/proportion	____	
TOTAL	____	

	VR I	VR II
CARD D		
Rectangles:		
1. Do not touch/intersect	____	____
2. Interior angles 90 degrees	____	____
3. Not rotated (15 degrees)	____	____
4. 2 small to right of large	____	____
5. Uppermost is taller	____	____
6. Bases of large and small level	____	____
7. Top of large higher than small	____	____
8. Bases of 3 equally long	____	____
9. Height of large > width	____	____
10. Heights of small < width	____	____
Circle Segment:		
11. Figure to right of rectangles	____	____
12. Arc curves to right	____	____
13. Symmetry/proportion	____	____
14. Not rotated (15 degrees)	____	____
Triangle:		
15. Figure to right of segment	____	____
16. Vertex touches midpoint	____	____
17. Contains 90 degree angle	____	____
18. Not rotated (15 degrees)	____	____
TOTAL	____	____
Total (Cards A through D) Max. = 41	____	____

Notes:

ORE CARD D - This next one is a little harder because it has two drawings on it. I want you to loc
in you will have just 10 seconds to look at the card. Then I will take it away and you will make both
e the drawing on the left side of the card here. (POINT) Make the drawing on the right side of the ca
.) (REMOVE) Now go ahead and make the two drawings.

...carefully.
...n memory.
...e (POINT). - Ready? (TURN OVER-10

.OW AT LEAST 10 SEC. TO ELAPSE BEFORE BEGINNING THE NEXT SUBTEST.

FORWARD - I am going to say a group of numbers. Listen carefully, and when I'm through, say them right after me. (PAUSE - SEC. - SEC.)

IGIT SPAN Discontinue after failure on both trials of any item.
Administer both trials of each item, even if the first trial is passed.

IGITS FORWARD					Score
Item	Trial I	Pass-Fail	Trial II	Pass-Fail	2, 1, or 0
1.	6-2-9		3-7-5		
2.	5-4-1-7		8-3-9-6		
3.	3-6-9-2-5		6-9-4-7-1		
4.	9-1-8-4-2-7		6-3-5-4-8-2		
5.	1-2-8-5-3-4-6		2-8-1-4-9-7-5		
6.	3-8-2-9-5-1-7-4		5-9-1-8-2-6-4-7		

Max. = 12

BACKWARD - Now I'm going to say some more numbers, but this time when I finish each group I want you to say them backwards. For example, if I say 2-4-3, what would you say? RESPOND - "that's right."
(OR, IF INCORRECT - "No, I said 2-3-4, so to say them backwards you would need to say 3-2-4.
Now try these numbers. Remember, you are to say them backwards. Ready? 1-5-8.) (GIVE NO SUBSEQUENT HELP)

Item	Trial I	Pass-Fail	Trial II	Pass-Fail	2, 1, or 0
1.	5-1		3-8		
2.	4-9-3		5-2-6		
3.	3-8-1-4		1-7-9-5		
4.	6-2-9-7-2		4-8-5-2-7		
5.	7-1-5-2-8-6		8-3-1-9-6-4		
6.	4-7-3-9-1-2-8		8-1-2-9-3-6-5		

Max. = 12 Total Backward | Max. Total = 24

VISUAL MEMORY SPAN (MATERIALS: BLOCK CARDS) FORWARD - (PRESENT CARD 1, RED BLOCKS, FACE DOWN)
(POINT TOWARDS CARD) On the other side of this card are a number of red squares.
When I turn the card face up, I will touch some of the squares, one after another.
Watch carefully as I do it, because as soon as I'm through, I'll ask you to touch the same squares as I did - in the same order.
(TURN CARD 1 OVER) 1A. Watch me. (TOUCH ONE SQUARE PER SEC.) (PAUSE 2 SEC. AND SAY.-) Now you do it. Touch the same squares I did in the same order.
1B. Now we'll do another one. First watch me, then you touch the same squares I do in the same order.
2A. Let's try one that's a little harder. (REPEAT IN SAME MANNER)

Item	Trial I	Pass-Fail	Trial II	Pass-Fail	2, 1, or 0
1.	2-6		8-4		
2.	2-7-5		8-1-6		
3.	3-2-8-4		2-6-1-5		
4.	5-3-4-6-1		3-5-1-7-2		
5.	1-7-2-8-5-4		7-3-6-1-4-8		
6.	8-2-5-3-4-1-6		4-2-6-8-3-7-5		
7.	7-5-6-3-8-7-4-2		1-6-7-4-2-8-5-3		

Max. = 14 Total Forward

TAPPING BACKWARD Administer Tapping Backward even if examinee scores 0 on Tapping Forward.					Score
Item	Trial I	Pass-Fail	Trial II	Pass-Fail	2, 1, or 0
1.	3-6		7-4		
2.	6-8-5		3-1-8		
3.	8-4-1-6		5-2-4-1		
4.	4-6-8-5-2		8-1-6-3-7		
5.	7-1-8-3-6-2		3-8-1-7-5-4		
6.	1-5-2-7-4-3-8		6-7-4-3-1-5-2		

BACKWARD - (PRESENT CARD 2, GREEN BLOCKS, FACE DOWN B-18
This card contains a number of squares like those on the card we jus
In this test I'm going to touch the squares one at a time as I did before.
But this time when I'm through I want you to touch the squares in reverse order.
(TURN CARD 2 OVER) 1A. Watch me. (TAP 2-7) Now you do it. Touch the same squares that I did but in reverse order. (RESPOND) That's right.
(IF NOT BACKWARD) Remember, on this part of the test you have to repeat them backward
(IF STILL WRONG) No, I touched this square first (TAP SQUARE 2) and then this square (TAP SQUARE 7). You are to touch them backwards.
like this (TAP 7 THEN 2). (GIVE 2ND PRACTICE TRIAL - TAP 8-1.) Now, you touch them in reverse order.

going to read you a little story which is just a few lines long.
en carefully and try to remember it just the way I say it - As close to the same words as you can remember.
en I m through, I want you to tell me everything I read to you. You should tell me as you can remember, even if you're not sure (of it).
you ready? Okay.

Healthy Elderly Study

Testing ended at:_____

Subject # _____
Date _____
Session # ____
Examiner _____

Delayed **Paragraph recall -- Set II**

Dogs / are trained / to find / the wounded / in war time. / Police dogs / are also trained/ to rescue / drowning people. / Instead of running / down to the water / and striking out,/ they are taught / to make / a flying leap / by which they save / many swimming strokes/ and valuable / seconds of time. / The European / sheep dog / makes the best / police / dog.

Total:_____

Total:_____

ow, what did I read to you? - Tell me everything and begin at the beginning.

ow I'm going to read you another little story. See how much of this one you can remember.
s with the first story, try to remember it just the way I say it. Ready? Okay. -

Many / school / children / in northern / France / were killed / or fatally hurt / and others / seriously injured / when a shell / wrecked / the schoolhouse / in their village. / The children / were thrown / down a hillside / and across / a ravine / a long distance / from the schoolhouse. / Only two / children / escaped uninjured.

Total:_____

1 + 2 = _____

Now, what did I read to you? - Tell me everything and begin at the beginning.

ALLOW AT LEAST 10 SEC. TO ELAPSE BEFORE STARTING THE NEXT SUBTEST

first word is OBEY. What word went with it? (ALLOW A MAX. OF 10 SEC. THEN CONTINUE - DO NOT CORRECT)

Time tested: _____
Delay:

Subject # _____
Date _____
Examiner _____

Paired Assiociates II - Delayed Recall

_____ Necktie - Cracker
_____ Come - Go
_____ Country - France
_____ In - Although
_____ Murder - Crime
_____ Lead - Pencil
_____ Lock - Door
_____ Knife - Sharp
_____ Dig - Guilty
_____ Jury - Eagle

_____ Total Hard
_____ Total Easy x 2
_____ **Total Score**

MATERIALS: SMALL SPIRAL AND FOLDER B
A little while ago I showed you some figures, each one paired with a different color. (PLACE FOLDER B OPENED IN FRONT OF S.) These were the colors.
Now I'm going to show you the figures again, and you try to remember which color went with each one.
(PUT SMALL SPIRAL IN FRONT OF S. AND OPEN TO LAST DIVIDER - SUBTEST 10) (TURN OVER 1ST CARD)
Here is the first figure. Look at these colors (POINT TO FOLDER B) and point to the one that goes with this figure (ALLOW 10 SEC. - DO NOT CORRECT)
(TURN PAGE) Which color goes with this figure? Point to it.
(REPEAT INSTRUCTIONS FOR ALL 6 CARDS - DO NOT CORRECT)

VISUAL PAIRED ASSOCIATES II			
Item	Key	Response	Score 1 or 0
1	Pk		
2	R		
3	G		
4	B		
5	Y		
6	Pu		
		Max. = 6 Total	

ould like you to look at each card, read the word out loud, and study the word until I take the card away.
ar you have seen and read all of the cards. I will ask you to tell me as many words as you can remember seeing and reading.
hat point, I will remind you of any words you did not remember.
will be going this test a number of times, so you will have plenty of chances to learn the words. Any questions?
HOW EACH CARD FOR 5 SEC. - CORRECT MISPRONUNCIATIONS.)
w I would like you to tell me all of the words in any order. (AFTER 60 SEC. WITH NO NEW WORDS:)
e words you did not remember were...
w I would like you to tell me all the words you can remember, including the ones I did not remind you of, in any order.
ONTINUE FOR 5 TRIALS. ON THE LAST TRIAL, REMIND THE S. OF WORDS NOT GIVEN.)

Subject # _____
Date _____
Examiner _____

Selective Reminding Test : II

Trial:	1	2	3	4	5	6	Total
egg							
runway							
fort							
toothache							
drown							
baby							
lava							
damp							
pure							
vote							
strip							
truth							

Intrusions:
(list)

	1	2	3	4	5	6	Totals
# recall							
LTR							
STR							
LTS							
CR							
CLTR							
RLTR							
reminders							
intrusions							
cum. int							

For the next few minutes, I'm going to ask you to list as many things as you can think of that belong to different categories.
(ALLOW 60 SEC. FOR EACH CATEGORY)

Healthy Elderly Study

Patient Identification Number _____

Date _____

Examiner's Initials _____

CATEGORY FLUENCY: I

First I would like you to list as many animals as you can think of. They can be animals of any kind, that live anywhere - on land, in the water, in the air, on a farm, in the zoo, whatever. Just list as many different animals as you can think of.

Now we will switch to the category clothing. I would like you to list as many pieces of clothing as you can. Men's, women's, children's, indoor, outdoor, whatever. Go ahead.

Now I would like you to list as many kinds of fruit as you can think of. Go ahead.

	ANIMALS	CLOTHING	FRUITS
15"			
30"			
45"			
60"			

	ANIMALS	CLOTHING	FRUITS
Total Output	____	____	____
Total Correct	____	____	____
Perseveration	____	____	____
Non-Words	____	____	____
Other Categories	____	____	____

Patient Identification Number _____

Date _____

Examiner's Initials _____

CATEGORY FLUENCY: II

Now I would like you to list as many first names of people as you can. They can be mens or women's names. People you know or don't know. Go ahead.

Now I would like you to list as many kinds of vegetables as you can. Go ahead.

	FIRST NAMES	VEGETABLES
15"		
30"		
45"		
60"		

	FIRST NAMES	VEGETABLES
Total Output	____	____
Total Correct	____	____
Perseveration	____	____
Non-Words	____	____
Other Categories	____	____

:de while ago you read some words on cards. remembered them, and told them to me. I reminded you of the words you forgot.
you remember that last? (PAUSE) Now I would like you to tell me all of the words you can remember from that list.
:F ALL WORDS NOT RECALLED:)
the words you did not remember. I am going to read you 4 words. One of the 4 words was on the list.
ould like you to listen to all four words. & then tell me which one you think was on the list. I would like you to guess if you're not quite sure.

Healthy Elderly Study

Subject # _____
Date _____
Examiner _____

SRT II: Recogntion

egg	egg	shell	beg	source
runway	airline	runner	darling	runway
fort	fort	castle	sink	fork
toothache	boldness	dentist	toothache	headache
drown	blown	drown	float	rib
baby	body	infant	middle	baby
lava	larva	lava	echo	rock
damp	damp	moist	hook	stamp
pure	purse	clean	pure	bare
vote	ballot	vote	dish	note
strip	chain	peal	strip	slip
truth	trust	rice	fact	truth

____ recall correct. Intrusions:

____ recognition correct.

____ total delayed correct.

Appendix C

Mood Questionnaires:

POMS
MAACL-R
BDI
GDS

Score Sheet - Mood Measures

Subject _____

POMS:

1. Elated-Depressed _____
2. Clearheaded-Confused _____
3. Energetic-Tired _____
4. Composed-Anxious _____
5. Confident-Unsure _____
6. Agreeable-Hostile _____

MAACL:

1. Anxious _____
2. Depressed _____
3. Hostile _____
4. Positive Affect _____
6. S. Seeking _____

GDS _____

BDI _____

I.D.#: _____ Examiner: _____ Date: _____

Below are words that describe feelings and moods people have. Please read EVERY word carefully. Then, for each word, check off ONE space under the answer which best describes how you have been feeling DURING THE PAST WEEK, INCLUDING TODAY.

Suppose the word is *happy*. Mark the one answer which is closest to how you have been feeling DURING THE PAST WEEK, INCLUDING TODAY.

	Much unlike this	Slightly unlike this	Slightly like this	Much like this
1. Composed				
2. Angry				
3. Cheerful				
4. Weak				
5. Tense				
6. Confused				
7. Lively				
8. Sad				
9. Friendly				
10. Tired				
11. Strong				
12. Clearheaded				
13. Untroubled				
14. Grouchy				
15. Playful				
16. Timid				
17. Nervous				
18. Mixed-up				
19. Vigorous				
20. Dejected				
21. Kindly				
22. Fatigued				
23. Bold				
24. Efficient				
25. Peaceful				
26. Furious				
27. Lighthearted				
28. Unsure				
29. Jittery				
30. Bewildered				
31. Energetic				
32. Lonely				
33. Sympathetic				
34. Exhausted				
35. Powerful				
36. Attentive				

	Much unlike this	Slightly unlike this	Slightly like this	Much like this
37. Serene				
38. Bad tempered				
39. Joyful				
40. Self-doubting				
41. Shaky				
42. Perplexed				
43. Active				
44. Downhearted				
45. Agreeable				
46. Sluggish				
47. Forceful				
48. Able to concentrate				
49. Calm				
50. Mad				
51. Jolly				
52. Uncertain				
53. Anxious				
54. Muddled				
55. Ready-to-go				
56. Discouraged				
57. Good-natured				
58. Weary				
59. Confident				
60. Businesslike				
61. Relaxed				
62. Annoyed				
63. Elated				
64. Inadequate				
65. Uneasy				
66. Dazed				
67. Full of pep				
68. Gloomy				
69. Affectionate				
70. Drowsy				
71. Self-assured				
72. Mentally alert				

I.D.#: _____ Examiner: _____ Date: _____

On this sheet you will find words which describe different kinds of moods and feelings. Make a check mark (✓) in the circles beside the words which describe how you feel now - today. Some of the words may sound alike, but we want you to check all the words that describe your feelings. Work rapidly.

1. O active
2. O adventurous
3. O affectionate
4. O afraid
5. O agitated
6. O agreeable
7. O aggressive
8. O alive
9. O alone
10. O amiable
11. O amused
12. O angry
13. O annoyed
14. O awful
15. O bashful
16. O bitter
17. O blue
18. O bored
19. O calm
20. O cautious
21. O cheerful
22. O clean
23. O complaining
24. O contented
25. O contrary
26. O cool
27. O cooperative
28. O critical
29. O cross
30. O cruel
31. O daring
32. O desperate
33. O destroyed
34. O devoted
35. O disagreeable
36. O discontented
37. O discouraged
38. O disgusted
39. O displeased
40. O energetic
41. O enraged
42. O enthusiastic
43. O fearful
44. O fine
45. O fit
46. O forlorn
47. O frank
48. O free
49. O friendly
50. O frightened
51. O furious
52. O lively
53. O gentle
54. O glad
55. O gloomy
56. O good
57. O good-natured
58. O grim
59. O happy
60. O healthy
61. O hopeless
62. O hostile
63. O impatient
64. O incensed
65. O indignant
66. O inspired
67. O interested
68. O irritated
69. O jealous
70. O joyful
71. O kindly
72. O lonely
73. O lost
74. O loving
75. O low
76. O lucky
77. O mad
78. O mean
79. O meek
80. O merry
81. O mild
82. O miserable
83. O nervous
84. O obliging
85. O offended
86. O outraged
87. O panicky
88. O patient
89. O peaceful
90. O pleased
91. O pleasant
92. O polite
93. O powerful
94. O quiet
95. O reckless
96. O rejected
97. O rough
98. O sad
99. O safe
100. O satisfied
101. O secure
102. O shaky
103. O shy
104. O soothed
105. O steady
106. O stubborn
107. O stormy
108. O strong
109. O suffering
110. O sullen
111. O sunk
112. O sympathetic
113. O tame
114. O tender
115. O tense
116. O terrible
117. O terrified
118. O thoughtful
119. O timid
120. O tormented
121. O understanding
122. O unhappy
123. O unsociable
124. O upset
125. O vexed
126. O warm
127. O whole
128. O wild
129. O willful
130. O wilted
131. O worrying
132. O young

I.D.#: _____ Examiner: _____ Date: _____

On this questionnaire are groups of statements. Please pick out the one statement in each group which best describes the way you feel today, that is, right now. Be sure to read all statements in the group before making your choice for that group. Then, place a check (✓) to the left of the statement which best describes the way you feel right now. If none of the statements in a group fits exactly the way you feel, then select the one which is closest. Do not skip any groups.

1. ___ I do not feel sad.
___ I feel sad.
___ I am sad all the time and I can't snap out of it.
___ I am so sad or unhappy that I can't stand it.

2. ___ I am not particularly discouraged about the future.
___ I feel discouraged about the future.
___ I feel I have nothing to look forward to.
___ I feel that the future is hopeless and that things cannot improve.

3. ___ I do not feel like a failure.
___ I feel I have failed more than the average person.
___ As I look back on my life, all I can see is a lot of failures.
___ I feel I am a complete failure as a person.

4. ___ I get as much satisfaction out of things as I used to.
___ I don't enjoy things the way I used to.
___ I don't get real satisfaction out of anything anymore.
___ I am dissatisfied or bored with everything.

5. ___ I don't feel particularly guilty.
___ I feel guilty a good part of the time.
___ I feel quite guilty most of the time.
___ I feel guilty all of the time.

6. ___ I don't feel I am being punished.
___ I feel I may be punished.
___ I expect to be punished.
___ I feel I am being punished.

7. ___ I don't feel disappointed in myself.
___ I am disappointed in myself.
___ I am disgusted with myself.
___ I hate myself.

8. ___ I don't feel I am any worse than anybody else.
___ I am critical of myself for my weaknesses or mistakes.
___ I blame myself all the time for my faults.
___ I blame myself for everything bad that happens.

9. ___ I don't have any thoughts of killing myself.
___ I have thoughts of killing myself, but I would not carry them out.
___ I would like to kill myself.
___ I would kill myself if I had the chance.

10. ___ I don't cry anymore than usual.
___ I cry more now than I used to.
___ I cry all the time now.
___ I used to be able to cry, but now I can't cry even though I want to.

11. ___ I am no more irritated now than I ever am.
___ I get annoyed or irritated more easily than I used to.
___ I feel irritated all the time now.
___ I don't get irritated at all by the things that used to irritate me.

12. ___ I have not lost interest in other people.
___ I am less interested in other people than I used to be.
___ I have lost most of my interest in other people.
___ I have lost all of my interest in other people.

13. ___ I make decisions about as well as I ever could.
___ I put off making decisions more than I used to.
___ I have greater difficulty in making decisions than before.
___ I can't make decisions at all anymore.

14. ___ I don't feel I look any worse than I used to.
___ I am worried that I am looking old and unattractive.
___ I feel that there are permanent changes in my appearance that make me look unattractive.
___ I believe that I look ugly.

15. ___ I can work about as well as before.
___ It takes an extra effort to get started at doing something.
___ I have to push myself very hard to do anything.
___ I can't do any work at all.

16. ___ I can sleep as well as usual.
___ I don't sleep as well as I used to.
___ I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
___ I wake up several hours earlier than I used to and find it hard to get back to sleep.

17. ___ I don't get more tired than usual.
___ I get tired more easily than I used to.
___ I get tired from doing almost anything.
___ I am too tired to do anything.

18. ___ My appetite is no worse than usual.
___ My appetite is not as good as it used to be.
___ My appetite is much worse now.
___ I have no appetite at all anymore.

19. ___ I haven't lost much weight, if any, lately.
___ I have lost more than 5 pounds.
___ I have lost more than 10 pounds.
___ I have lost more than 15 pounds.
I am purposely trying to lose weight by eating less. Yes___ No ___

20. ___ I am no more worried about my health than usual.
___ I am worried about physical problems such as aches and pains; upset stomach; or constipation.
___ I am very worried about physical problems and it's hard to think of much else.
___ I am so worried about my physical problems that I cannot think about anything else.

21. ___ I have not noticed any recent change in my interest in sex.
___ I am less interested in sex than I used to be.
___ I am much less interested in sex now.
___ I have lost interest in sex completely

I.D.#: _____ Examiner: _____ Date: _____

Circle the best answer (yes or no) for how you felt over the past week.

1. Are you basically satisfied with your life? ..... yes no
2. Have you dropped many of your activities and interests? ..... yes no
3. Do you feel that your life is empty? ..... yes no
4. Do you often get bored? ..... yes no
5. Are you hopeful about the future? ..... yes no
6. Are you bothered by thoughts you can't get out of your head? ..... yes no
7. Are you in good spirits most of the time? ..... yes no
8. Are you afraid that something bad is going to happen to you? ..... yes no
9. Do you feel happy most of the time? ..... yes no
10. Do you often feel helpless? ..... yes no
11. Do you often get restless and fidgety? ..... yes no
13. Do you frequently worry about the future? ..... yes no
14. Do you feel you have more problems with memory than most? ..... yes no
15. Do you think it is wonderful to be alive now? ..... yes no
16. Do you often feel downhearted and blue? ..... yes no
17. Do you feel pretty worthless the way you are now? ..... yes no
18. Do you worry a lot about the past? ..... yes no
19. Do you find life very exciting? ..... yes no
20. Is it hard for you to get started on new projects? ..... yes no
21. Do you feel full of energy? ..... yes no
22. Do you feel that your situation is hopeless? ..... yes no
23. Do you think that most people are better off than you are? ..... yes no
24. Do you frequently get upset over little things? ..... yes no
25. Do you frequently feel like crying? ..... yes no
26. Do you have trouble concentrating? ..... yes no
27. Do you enjoy getting up in the morning? ..... yes no
28. Do you prefer to avoid social gatherings? ..... yes no
29. Is it easy for you to make decisions? ..... yes no
30. Is your mind as clear as it used to be? ..... yes no

Appendix D

Rivermead Behavioural Memory Test Forms

SCORESHEET - RBMT

SUBJECT NO._____ OLD SUBJECT NO. _____ DATE _____

	Raw Score	Profile Score (/2)
First name. Second name	_____	_____
Belonging	_____	_____
Appointment	_____	_____
Pictures	_____	_____
Story (immediate)	_____	_____
(delayed)	_____	_____
Faces	_____	_____
Route (immediate)	_____	_____
(delayed)	_____	_____
Message (add imm. & delay)	_____	_____
Orientation	_____	_____
Date	_____	_____
	Total (max. 24):	_____

RBMT SUBJECT_____ DATE_____

Item 1 & 2 - First and Second Name

What I want you to do is remember this person's name (show photo). Her name is Catherine Taylor. Would you repeat that name, please? Later on I am going to ask you what her name is. (place photo downwards on table)

Item 3 - Belonging

What I am going to do now is to put something of yours away, and see if you will remember to ask me for it when I say we have finished this test. I also want you to remember where I put it. Can You let me have a personal item such as a comb, pencil or hankie? When I say "we have finished this test", I want you to ask me for your ( ) and to tell me where I put it.

Item 4 - Appointment

I am going to set this alarm to go off in 20 minutes. When it rings I want you to ask me when you will know the results of this test. Just say something like "Can you tell me when I will know the results from this test?" or words to that effect.

Item 5 - Pictures

Now I am going to show you some pictures that I want you to remember. Look at each one carefully and tell me what object is pictured. I shall show you each one for five seconds to give you a chance to memorize it. Later on I am going to show you more pictures and I want you to pick out the ones I have just shown you .

Item 6 - Story (immediate)

Next I am going to read you a newspaper story of about five or six lines. Listen carefully and when I have finished tell me back as much as you can remember. Ready –

Mr. Brian / Kelly / a Pinkerton employee / was shot dead / on Monday / during a bank robbery / in Toronto. / The four robbers / all wore masks / and one carried / a sawed-off / shotgun. / Police detectives / were sifting through / eye-witness accounts / last night./ A police sopkesperson said / "He was a very brave man. / He went for / the armed robber / and put up a hell of a fight".

Raw Score _____

Now tell me back as much of the story as you can, in as close to the same words as possible.

Item 5 - Pictures

Now we are going back to those pictures I showed you earlier. For each picture I want you to tell me whether you saw it before or not. (show 20 pictures - 10 new, 10 shown, unpaced, encourage guessing if necessary)

Correct?

1_____	6_____
2_____	7_____
3_____	8_____
4_____	9_____
5_____	10_____

Total_____
False Positives_____
Raw Score _____

Item 7 - Faces

This time I am going to show you some faces. I'd like you to look at each one carefully, and tell me if the person is male or female. Also tell me if the person is under or over 40 years of age. This is just to help you concentrate since you will have to remember them later on. (show each of 5 pics. for 5 secs. each)

Item 8a - Route (immediate)

What I am going to do now is trace a short path around this room. I'd like you to watch what I do, and when I have finished, do the same thing. I am going to start form the door, and take this envelope with me. (show envelope to S). From here I am going over to the window (go), and then from the window to the counter. I am going to leave this envelope on the counter, and from here I am going to the chair, and from the chair back to the door. (retrieve envelope to back in original place in from of Ss and sit back down). Now what I would like you to do is to start where I started and follow the same path.

Door_____ Raw Score_____
Window_____
Counter_____
Chair_____
Door_____

Item 9a - Message (immediate)

(If Ss did not pick up envelope, stop them from continuing) I took something with me. Remember what it was? (if not) It was this envelope. Do what I did with it.

picked up spontaneously _____
picked up after prompt _____
left in correct location _____

Raw score _____

Item 7 - Faces

Now we are going back to those faces I showed you earlier. For each face I want you to tell me whether you say it before or not. (10 faces, 5 new, unpaced, guess if unsure)

1_____
2_____
3_____ Total _____
4_____ False Positives _____
5_____ Raw Score _____

Items 10 and 11 - Orientation and Date

What year is it now? _____
What Month is it? _____
What day of the week? _____
What date? _____
What place are we in? _____
What city? _____
How old are you? _____
What year were you born? _____
Who is the PM? _____
Who is the US President? _____

Raw Score _____

(engage in conversation until the alarm sounds.)

Item 4 - Appointment
(alarm rings - if S does not ask spontaneously) What were you going to do when the alarm rang?

Spontaneous _____
w/ prompt _____
remembered had to ask something but couldn't remember what _____

Raw Score _____

Item 6b - Story (delayed)
Do you remember that newspaper story I read to you earlier? I would like to know how much of it you can remember now. Tell me just as much as you can. (if remembers nothing - provide clue) It started off - "Mr. Brian Kelly, a Pinkerton employee...."

Mr. Brian / Kelly / a Pinkerton employee / was shot dead / on Monday / during a bank robbery / in Toronto. / The four robbers / all wore masks / and one carried / a sawed-off / shotgun. / Police detectives / were sifting through / eye-witness accounts / last night./ A police sopkesperson said / "He was a very brave man. / He went for / the armed robber / and put up a hell of a fight".

Raw Score _____

Item 8b - Route (delayed)

Remember the path I took around the room earlier? I would like to see if you can still remember it. So could you start where I started and please take the same route as I took?

Door _____
Window_____
Counter_____
Chair _____
Door _____ Raw score _____

9b - message (delayed)

(If not spontaneously picked up - stop subject from continuing) I took something with me. Do you remember what it was? (if not) It was this envelope: do what I did with it.

Picked up spontaneously _____
picked up after prompt _____
Left at correct location _____

Raw score _____

Items 1 & 2 - First and Second name

(re-present first photograph) Do you remember this woman's name? (if not) her first name began with a "C" (second name not spontaneously recalled or is wrong). Her second name began with a "T". (or) no, but it did begin with a "T".

First Name correct no prompt _____
correct w/ prompt _____ Raw Score _____
Last Name correct no prompt _____
correct w/ prompt _____ Raw Score _____

Item 3 - Belonging

We have finished this test. (pause for 5 seconds). You were going to remind me to give you something of yours. Do you remember what it was? (if still doesn't spontaneously say where it was). Do you remember where I put it?

Place: without prompt _____
with prompt _____
Item: without prompt _____
with prompt _____

Raw score _____

RBMT - Scoring Guide

1/2. First Name + Second Name

without prompt = 2
with prompt = 1

Raw score:	<2	3	4
profile score:	0	1	2

3. Belonging (place/item)

without prompt =2
with prompt =1

Raw score:	<2	3	4
profile score	0	1	2

4. Appointment

spontaneous =2
with prompt =1
remembered something but not what =1

5. Pictures

Raw = correct - false positives

Raw score:	<8	9	10
Profile score:	0	1	2

6. Story

Each idea or close synonym = 1
Each partial or aprox. synonym = 1/2

Raw score:	<3.5	4-5.5	>6
Profile score:	0	1	2

7. Faces

Raw = correct - false positives

Raw Score:	<3	4	5
Profile score:	0	1	2

8. Route (imm + delay) – separately

Raw = total stages correct

Raw score:	<3	4	5
Profile score:	0	1	2

9. Message (imm + delay)

picked up spontaneously = 2
picked up after prompt = 1
left in correct location = another 1

Add imm. + delay

Raw score:	<4	5	6
profile score	0	1	2

10. Orientation

Raw score:	<7	8	9
Profile score:	0	1	2

11. Date

Raw score:	> 2 days off	1 day off	correct
Profile score:	0	1	2

Appendix E

Study 2 Consent Form

Jewish General Hospital
Memory Clinic/Division of Geriatrics

RELATIONSHIPS BETWEEN HORMONE LEVELS AND EVERYDAY MEMORY PERFORMANCE IN PATIENTS WITH MEMORY PROBLEMS COMPARED TO HEALTHY ELDERLY CONTROLS

INFORMATION AND CONSENT FORM

Your doctor has referred you to us because he/she has determined that you have problems with your memory.

Objectives of the Study

We are undertaking a study to determine if hormone levels are different in people with memory problems when compared to people of the same age who do not have problems with memory, and to look at how people with memory problems perform on tests that measure everyday memory tasks. We are inviting you to participate in this study and wish to describe what your participation will involve.

Procedure

During your annual visit to the Memory Clinic at the Jewish General Hospital, we will perform a number of paper and pencil tests of everyday memory that involve remembering names, faces and everyday objects and events. This will take about 30 minutes. A small, 10mL blood sample (about one tablespoon) will be taken by a registered nurse at the time of your visit to measure your hormone levels. There is no other medical procedure involved. You and a companion will be compensated for expenses incurred from your visit. We will also be looking in your file from the memory clinic at the results of other memory tests you have already taken.

Disadvantages of Participating in the Study

The blood test involves taking a tube of blood from your arm with a standard needle puncture. As with any blood test, some people develop a slight bruise on their arm which should disappear in a few days.

RELATIONSHIPS BETWEEN HORMONE LEVELS AND EVERYDAY MEMORY PERFORMANCE IN PATIENTS WITH MEMORY PROBLEMS COMPARED TO HEALTHY ELDERLY CONTROLS

Confidentiality

The results of my blood tests and memory tests will be strictly confidential - only a number assigned to me will appear on all test forms but not my name. The investigators would be pleased to share the test results with me at the completion of the study if that is what I would like.

Discontinuation

I am free to discontinue the testing session for any reason or at any time. In this event, I will still receive compensation for my travel expenses.

Patient Rights

I have had this study explained to me, and had my questions answered to my satisfaction. A copy of this consent form will be given to me.

The following is the name, address and telephone number of the Hospital's Patient Representative, who is not associated with this study and to whom I may address my concerns about this study: **Ms. Roslyn Davidson, 3755 Cote Ste. Catherine Road, Montreal, H3T-1E2, 340-8222, ext. 5833**

The following is the name, address and telephone number of the researchers whom I may contact for answers to questions about the research or any injuries or adverse reactions which may occur: **Dr. Barbara Sherwin, McGill University, 1205 Dr. Penfield Ave, Montreal, 398-6087 or Jewish General Hospital, 340-8222 (ext. 5870), Linda E. Carlson, McGill University, 1205 Dr. Penfield Ave, Montreal, 398-6145**

RELATIONSHIPS BETWEEN HORMONE LEVELS AND EVERYDAY MEMORY PERFORMANCE IN PATIENTS WITH MEMORY PROBLEMS COMPARED TO HEALTHY ELDERLY CONTROLS

Signature

I have read and I understand the above information, have had the study explained to me and my questions have been answered to my satisfaction. I agree to take part in the study being conducted by Dr. Barbara B. Sherwin, Linda E. Carlson & Dr. Howard Chertkow.

I agree to take part in this study. _____YES _____NO

SIGNATURE	PRINT NAME	DATE
SIGNATURE OF INVESTIGATOR	PRINT NAME	
SIGNATURE OF PERSON EXPLAINING INFORMED CONSENT	PRINT NAME	
SIGNATURE OF CAREGIVER	PRINT NAME	