MENOPAUSE, MOOD AND MEMORY: THE EFFECT OF HORMONE REPLACEMENT THERAPY ON MOOD AND EVERYDAY MEMORY IN MID-LIFE WOMEN

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ABSTRACT

There is considerable neuro-scientific evidence that oestrogen influences memory and enhances mood because of its influence on brain mechanisms. Research on the effect of hormone replacement therapy (HRT) on both mood and memory is equivocal although findings indicate that oestrogen may enhance verbal memory. It has been suggested that this area of research should expand to include ecologically valid measures of everyday memory. This study examined the effect of HRT on mood and everyday memory in two separate samples of mid-life women. A cross-sectional comparison of HRT users and non-users among 124 women aged between 40 and 60 years showed that there were no significant differences in mood between HRT users and non-users. However, HRT users performed significantly better on tests of everyday memory and delayed verbal memory when the effects of age, IQ, and education were controlled for. A within-subjects comparison, using the same measures, with 17 women before, and 3 months after, HRT use, showed that negative mood states were reduced and positive mood states were enhanced by HRT, when change in stressful life events, self-rated health, sleep problems, vasomotor symptoms, and exercise were controlled for. The longitudinal sample also showed that everyday memory, working memory, and delayed verbal memory improved with HRT use. The improvement in memory was not mediated by mood. These results suggest that the effect of HRT on mood may only be short-term but that oestrogen does enhance everyday memory.

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CHAPTER 1

INTRODUCTION

Menopause is a natural and universal event in the human female cycle during which some women can experience symptoms of mood disturbance and the perception of decline in their memory function. While hormone replacement therapy was initially prescribed for mid-life women to alleviate the somatic symptoms of menopause, and subsequently to reduce the incidence of osteoporosis and heart disease in postmenopausal women, there is now considerable neuro-scientific evidence that oestrogen influences memory and enhances mood because of its influence on brain mechanisms.

The study of endocrine effects on cognition, which began in the 1970s, has accumulated substantial evidence to suggest that the hormones which organise and activate brain and behavioural mechanisms for reproductive behaviour also influence brain regions involved in learning and memory across the lifespan. In particular, there is now considerable evidence from research in the neurosciences that oestrogen influences cognitive functions associated with memory through its actions on brain structures such as the hippocampus and basal forebrain (McEwen, Alves, Bulloch & Weiland, 1997). In addition, there is also evidence to suggest that oestrogen enhances mood because of its influence on neurotransmitter mechanisms, in particular that of serotonin (Halbreich, 1997).

The alterations in the hormonal milieu which occur at menopause, primarily the cessation of the production of estradiol, combined with the clinical practice of prescribing hormone replacement therapy to women to relieve the symptoms of menopause, provides the opportunity for investigating the possible effects of oestrogen on mood and memory. Such research is important for mid-life women who experience mood and memory problems during menopause and for medical practitioners in the decision-making process regarding hormone replacement therapy.

The following three chapters introduce the concepts of menopause, mood and memory in relation to HRT use. Chapter 2 defines menopause from biological, psychological, social and cultural points of view and explains what hormone replacement therapy is, the various treatment regimens, and the goals of therapy. Chapters 3 and 4 look at mood and memory respectively: the relationship between these constructs and menopause, the theoretical explanations of change at menopause, reviews of associated literature, and the methodological issues involved in research. Chapter 5 summarises these introductory chapters.

CHAPTER 2

MENOPAUSE

2.1 *Menopause defined*

Menopause is a physiological event which occurs in all women who reach midlife. Scientifically, it is the permanent cessation of menstruation due to loss of ovarian follicular function and clinically, it is diagnosed after 12 months of amenorrhoea, so the time of the final menses is determined retrospectively. The average age at menopause is 51 years (Greendale, Lee, & Arriola, 1999). However, the word menopause is also used in a wider sense by the medical profession, researchers, and women themselves, to refer to a much longer period of between 2 and 8 years during which there is a complex transition involving biological, psychological, social and cultural factors. This transition period can also be referred to as the climacteric or perimenopause.

Biologically, perimenopause, the transition period from regular ovulatory menstrual cycles to complete cessation of ovulation, occurs when the neurohormonal systems that govern ovulation begin to become dysregulated leading to irregular menstrual cycles. During this transition, the physiological event which takes place is associated with complex hormonal change which results in plasma levels of oestrogen and progesterone decreasing and luteinizing hormone and follicle stimulating hormone increasing as a result of reduced estrogen levels (Ballinger, Browning, & Smith, 1987). It is argued that the physical symptoms experienced during this phase of life are related to reduced levels of oestrogen (Wilson, 1966). The only physical symptoms which research has shown to be directly associated with the menopause transition are vasomotor symptoms - hot flushes and night sweats (Greene, 1992; Greendale et al, 1999). Other physical

symptoms which research has associated with the physiological changes that occur after menopause, although they may more appropriately be associated with ageing, are urinary incontinence, urinary tract infection, vaginal atrophy, reduced sexual function, coronary heart disease and osteoporosis (Greendale et al, 1999).

Psychologically, the perimenopausal transition is concerned with women dealing with a changing internal hormonal environment and its associated loss of reproductive potential, together with the transition into mid- and later life. In addition to the effect that a decrease in oestrogen has on reproductive potential, it is also purported to have an influence on cognitive and affective functioning because of the role that this steroidal hormone is known to have on the brain (Sherwin, 1996). While the psychological symptoms of dysphoria and memory loss, which are frequently associated with menopause, may therefore have a neurobiological basis, their presence may also be related to the ageing process itself and, in the case of dysphoria, to the presence of physical symptoms.

Social and cultural factors which confront women during menopause relate to role changes and cultural attitudes towards ageing. Women may encounter role changes in the family through divorce, children leaving home, or elderly parents needing care. Various socio-demographic factors such as education level, occupational status, income and social network influence the way in which women cope with these role changes and how they experience menopause (Dennerstein, 1996). Cross-cultural studies indicate that menopause is experienced differently in different cultures. In cultures where women receive rights at the time of menopause that were denied them during their

child-bearing years, menopausal symptoms are minimal (Flint, 1975). The fact that Western societies are youth oriented and that stereotypes of midlife women are largely negative (Greer, 1991) does not serve to provide a supportive environment for menopausal women.

2.2 *Hormone replacement therapy (HRT)*

HRT is an umbrella term for the hormones prescribed by physicians to restore levels of oestrogen and progesterone during and after menopause. Current usage of HRT in developed countries is estimated at 20 million (Grant, Gray, Paoletti, Thomton & von Kleist, 1999) and research in New Zealand indicates a usage rate of 20% among women between the ages of 45-64 (North & Sharples, 2001).

Oestrogen replacement therapy (ERT) was introduced in the 1940s and became popular in the 1960s and 70s. It was introduced to relieve the physical symptoms of menopause but was advertised as a cure-all for problems of menopause and ageing; a fountain of youth for mid-life women (Coney, 1991). In the mid-1970s, it was discovered that postmenopausal women with a uterus who had been on ERT for seven years or longer were at risk of developing endometrial cancer (Ziel & Finkle, 1975). As a result of this finding and subsequent research, it is now recommended that women with a uterus be prescribed oestrogen in combination with the opposing hormone progestogen and that unopposed oestrogen be given only to women who have undergone a hysterectomy. However, it is the oestrogen component of HRT which is generally considered to be the 'active' ingredient; the hormone which is considered beneficial for women during and after menopause.

There are several types of oestrogen and progestogen used in HRT and a variety of treatment regimens used. Most of the hormone preparations used in HRT contain synthetically produced versions of naturally occuring female oestrogens which can be administered orally, vaginally, by patches, subcutaneous implant or injection. Progestogens are synthetic progesterones which are administered orally for the sole purpose of preventing endometrial cancer (Greendale et al, 1999). The three basic HRT regimens are: unopposed therapy (oestrogen alone); opposed sequential therapy, where a period of oestrogen is followed by a shorter period combined with progestogen; opposed continuous combined therapy, using both oestrogen and progestogen simultaneously. The most common administration of HRT is a daily, continuous oral dose of oestrogen with cyclical progestogen depending on gynaecological status (Smith & Hughes, 1998). The type of HRT and treatment regimen is determined by the physician in consultation with her/his female patient. It is dependent on the medical health of the woman, her reasons for taking HRT and any previous experience she has had with HRT.

HRT is a controversial therapy within the medical profession, between research disciplines and among women themselves. While there are both benefits and risks to HRT usage which are clinically researched and documented in medical literature, the medicalisation of menopause produced by the availability of HRT is a contentious issue and many of the claims made for its use are debated because of equivocal research results.

The main clinical goal of HRT, and an area in which there is relative consensus, is the alleviation of the physical symptoms of menopause. Clinical trials have shown reduction of vasomotor symptoms for all types of treatment although a substantial placebo effect has been identified (Grant et al, 1999). This goal indicates short-term use of HRT as physical symptoms decline after the menopause transition. Another area of medical research consensus is the prescription of HRT as a preventive measure against osteoporosis and cardiovascular disease, a long-term goal which indicates long-term usage to maintain the beneficial effect of oestrogen. However, this prophylactic use of HRT is controversial from the perspective of long-term medication of well women (Coney, 1991) and the increased risk of breast cancer (Grant et al, 1999).

Behavioural and affective symptoms such as fatigue, insomnia, loss of libido, inability to concentrate, forgetfulness, irritability and depression are complaints frequently associated with menopause. Research pertaining to the effect of HRT on these symptoms is equivocal, and that related specifically to mood and memory will be examined in greater detail in the following sections of this thesis. However, probably a reasonable summation of this research is that given by Utian (1987) who coined the phrase "mental tonic effect" to explain the lifting of mood provided by HRT and the subsequent alleviation of behavioural symptoms.

While HRT may be beneficial to many women with menopause problems and for the prevention of osteoporosis and cardiovascular disease, it should be noted that there are several medical contraindications to oestrogen use (Smith & Hughes, 1998); that there may be an increased risk of breast cancer (Grant et al, 1999); and that some women may

suffer unpleasant side effects from the medication (McKeon, 1990).

CHAPTER 3

MOOD

3.1 *Mood and menopause*

The psychiatric/psychological aspect of menopause which has been most frequently researched is that of mood disorders, particularly depression. The notion that there is a relationship between psychiatric disorder and reproductive physiology in women is an ancient one which is still strongly contested. Although the concepts of hysteria and involutional melancholia have been discarded, terms such as 'menopause-related mood syndrome' (Stone & Pearlstein, 1994) and 'menopause-related affective disorder' (Schmidt & Rubinow, 1991) are still used as umbrella terms for psychological symptoms such as depressed mood, decreased self-confidence, anxiety, insomnia and decreased libido which are frequently associated with menopause.

Research conducted to date on the relationship between menopausal status and mood disorder has, overall, provided only equivocal results. Reviews of the literature (eg Gath, 1998; Holte, 1998; Kaufert, 1990; Pearce, Hawton & Blake, 1995; Pearlstein, Rosen & Stone, 1997) agree that the equivocal nature of the research is due to methodological issues. The methodological issue of particular interest is that of sample selection. When studies are separated out into population/community or clinical samples, the literature reveals a level of consensus within each sample type.

The reviews of Pearce et al (1995) and Pearlstein et al (1997) agree that studies of women presenting at menopause clinics for the treatment of somatic or psychological symptoms, do have elevated depressive symptoms and a decreased quality of life. A

higher level of depressive symptoms in clinical samples is not unexpected in light of the fairly well established view that clinic attenders are not representative of the general population in terms of mental health. Attendance at clinics is determined by a wide variety of personal, social and cultural factors (Mechanic, 1986) and studies have confirmed that women who seek clinical help for menopausal symptoms differ on many variables from women of the same age and menopausal status who do not seek help (eg McKinlay, McKinlay & Brambilla, 1987; Morse et al,1994). Further, several studies have indicated that there is an association between gynaecological complaints and psychiatric morbidity: that women who attend gynaecology clinics or have undergone gynaecological surgery have increased rates of psychiatric disturbance (eg Ballinger, 1977; Hay, Bancroft & Johnstone, 1994; Worsley, Walters & Woods, 1977).

Pearce et al (1995) and Pearlstein et al (1997) also agree that most population studies, both longitudinal and cross-sectional report no increase in moderate or severe depressive symptoms with menopause. What these studies indicate is that menopausal status per se has little explanatory power for depressive symptoms in mid-life women. Rather, factors most frequently associated with depressive symptoms are prior depression, previous premenstrual syndrome, hysterectomy, vasomotor symptoms, psychosocial stressors, poor health status and lifestyle variables such as lack of exercise and smoking (Collins & Landgren, 1995; Dennerstein, 1996; McKinlay et al, 1987). However, two longitudinal studies suggest a modest increase in depressive symptoms during perimenopause (Avis, Brambilla & McKinlay, 1994; Hunter, 1990) and three cross-sectional studies indicate mild symptoms that peak in perimenopause (Lee & Taylor, 1996; McKinlay et al, 1987; Woods & Mitchell, 1997). These results may point

to an emotional reaction to the vasomotor symptoms which commonly occur during perimenopause.

3.2 *Aetiology of mood change during menopause*

Current theoretical explanations of the aetiology of mood disorders during menopause include neurobiological, domino and psychosocial theories (Schmidt & Rubinow, 1991).

3.2.1 Neurobiological Theory

The neurobiological theory (Halbreich, 1997) presumes that mood symptoms are secondary to changes in reproductive hormones. Oestrogen, in addition to its effects on the ovaries and peripheral secondary sex organs, also has far-reaching effects on neurotransmitter activity in the brain. In particular, oestrogen increases levels of norepinephrine, dopamine and serotonin, all of which are putatively involved in the regulation of mood and behaviour with lower levels of these neurotransmitters being associated with lower levels of affect. There are also indications from animal research (Mason, Taylor, Brady, & Tolliver, 1968) that oestrogen levels are lowered in response to psychological stressors and Ballinger (1990) found that lowered levels of oestrogen in postmenopausal women were associated with increases in psychological stress. Thus, the biological changes at menopause and those of stress are likely to interact and exacerbate each other.

3.2.2 Domino theory

The domino theory (Dennerstein & Van Hall, 1986) suggests that menopausal mood changes arise from the somatic symptoms that appear due to oestrogen decline.

According to this theory, dysphoria, decreased concentration and irritability which may occur during the menopause transition may be secondary to vasomotor-related sleep deprivation or to vasomotor symptoms themselves.

3.2.3 Psychosocial theory

The psychosocial theory (McKinlay et al, 1987) posits that mood changes occur in response to altered roles and relationships associated with age-related life changes in women. This theory presumes that the stress which may occur as a result of increased caretaking responsibilities for elderly parents, children leaving home, divorce, and health problems may coincide with the menopause transition and cause women to be particularly vulnerable to depression at this time

3.3 *HRT and mood*

The use of HRT to treat dysphoria during menopause is widely accepted within the medical profession (Barlow, 1991) but the literature concerning the effect of hormone replacement on mood is confusing, and extensive research has not yielded any uniformity of results. However, the results from several prospective clinical trials of both naturally and surgically postmenopausal women suggest that the administration of oestrogen does enhance mood in healthy nondepressed women.

In naturally menopausal women, placebo-controlled trials of oestrogen alone have demonstrated improved quality of life (Wiklund, Karlberg, & Mattson, 1993) and improved mood (Fedor-Freybergh, 1977; Klaiber, Broverman, Vogel, Peterson, & Snyder, 1997). Placebo-controlled trials of combined oestrogen and progesterone also

suggest improved mood (Derman, Dawood, & Stone, 1995; Purdie, Empson, Crichton, & MacDonald, 1995) although the addition of progesterone was found to attenuate the effect of oestrogen on mood (Sherwin, 1991; Sherwin & Gelfand, 1985), an effect counteracted by a higher dose of oestrogen. Controlled studies which have not demonstrated a positive effect of oestrogen on mood have frequently been those which have used samples of mixed menopausal status and/or women with depressive symptoms (e.g. Campbell & Whitehead, 1977; Pearce et al, 1997; Strickler et al, 1977). However, Girdler, O'Briant, Steege, Grewen, & Light (1999), in a placebo-controlled study of asymptomatic postmenopausal women with no depressive symptoms, concluded that the use of HRT was not associated with significant changes in mood.

Prospective treatment studies of HRT in surgically menopausal nondepressed women have also demonstrated a positive effect of oestrogen on mood. In a placebo-controlled double-blind study, Sherwin and Gelfand (1985) followed women prospectively through abdominal hysterectomy and oophorectomy, or hysterectomy only (to control for the surgical procedure itself), and found that women in the placebo group had higher depression scores than the groups treated with active hormone preparations (oestrogen and/or androgen) or the ovary-intact group. It was also found that the depression scores of the hormone-treated women increased during the placebo month between treatment phases when levels of estradiol were decreased. This finding of an association between positive mood and plasma levels of estradiol was confirmed in another study (Sherwin, 1988) which investigated mood differences in women who had undergone hysterectomy and oophorectomy approximately 4 years earlier. Those who had received oestrogen injections regularly for the previous 2 years had more positive moods than a matched

control group of women who had remained untreated since surgery. A placebo-controlled study which used a sample of women who were asymptomatic for vasomotor symptoms and two levels of oestrogen dosage (Ditkoff, Crary, Cristo & Lobo,1991) also found a positive effect of oestrogen on mood which was not dose-related. However, a placebo-controlled study by Phillips and Sherwin (1992) which was primarily designed to look at the effects of oestrogen on cognitive function found no effect of HRT on mood measures.

3.4 *Methodological issues*

As with the mood and menopause research, it is suggested that the equivocal nature of the HRT and mood studies is due to methodological issues. The reviews of literature by Gath (1998), Holte (1998) and Pearce et al (1995) indicate that both areas of research suffer from inconsistency in the definition and measurement of mood, control of the physical symptoms of menopause, and control for non-menopausal factors such as stress, health and exercise. As the HRT and mood research seeks to prove or disprove the neurobiological, domino or psychosocial theories, it is important that these issues are addressed.

3.4.1 Definition of mood

Research included in the body of literature on the effect of HRT on mood has used a range of psychological constructs which appear to come from different conceptual perspectives. Constructs such as quality of life (Wiklund et al, 1992), psychological wellbeing (France, Lee & Schofield, 1996), or mood (Klaiber et al, 1997) appear to be used when the psychological symptoms are regarded as being a consequence of the

menopause experience. Alternatively, other studies which use constructs of depressive symptoms (Palinkas & Barrett-Connor, 1992) or depression (Pearce et al, 1997) seem to assume that the psychological symptoms indicate a discrete psychological disorder. As there is strong evidence that menopausal status per se has little explanatory power for depressive symptoms in mid-life women (Pearce et al, 1995) the notion of psychological symptoms being a consequence of menopause would seem to be the appropriate conceptual definition to adopt.

Even when 'mood' has been the construct of research, a strong emphasis has been placed on depressed mood with little attention being paid to positive affect and other less clinical aspects of mood. People experience a wide range of moods, both positive and negative, and have a large repertoire of affective expressions so it would seem expedient to consider a broader range of mood states when investigating the effect of HRT on mood in a normal population.

3.4.2 Measurement of mood

The way in which mood has been measured has also lead to difficulty in the interpretation of results as a myriad of different measures have been used, some unstandardised. Even when standardised measures have been used, these have frequently been menopausal indices (e.g. Hunter, 1992; Sherwin 1988). While the reliability of such tools for measuring psychological symptoms has been established, their validity in terms of detection of psychological disorder has not. This limits the value of some studies designed to investigate depressed mood during menopause (Greene, 1984; McKinlay et al, 1987). Alternatively, self-report instruments of known

reliability and validity for detecting psychological disorder (e.g. Beck, Ward, Mendelson, Mock, & Erbaugh, 1961; Hamilton, 1967) which have frequently been used (e.g. Derman et al, 1995; Klaiber et al, 1997) present a criterion overlap of depression and menopause as they contain items relating to symptoms of hot flushes and sweating, and loss of interest in sex. This may lead to a nondepressed woman giving positive responses on a depression scale by virtue of being menopausal, or to a depressed woman giving positive answers in relation to menopausal symptoms, thus emphasising the importance of assessing mood states and menopausal symptoms with mutually exclusive instruments.

3.4.3 Mood and vasomotor symptoms

Another methodological issue which may account for the inconsistency of findings in the HRT and mood studies is the frequent lack of control for vasomotor symptoms. The strong association between vasomotor symptoms and depressed mood has been demonstrated in a number of studies (e.g. Collins & Landgren, 1995; Palinkas & Barrett-Connor, 1992) and, when effects of vasomotor complaints have been controlled for, no effect of menopause on depression has been found on naturally menopausal women. However, some of the studies which have concluded that HRT improves mood have failed to control for the effect of relieving vasomotor symptoms; thereby overlooking the confounding effect of these symptoms (e.g. Derman et al, 1995; Purdie et al, 1995; Sherwin, 1988). In studies where such control was present (e.g. Dennerstein, Burrows, Hyman, & Sharpe, 1979; Wiklund et al, 1992) the elevated affective state following HRT was correlated with relief of vasomotor symptoms indicating support for the 'domino effect': the improvement in negative mood was

secondary to the alleviation of physical symptoms by oestrogen.

3.4.4 Mood and stress, exercise and health status

Other factors highly relevant to the HRT and mood research which are frequently overlooked are those of stress, exercise, and health status. Several studies have demonstrated (e.g. Avis et al, 1994; Hunter, 1992; Kaufert, Gilbert, & Tate, 1992) that stress is the most influential factor in accounting for depressed mood in mid-life women. It has also been identified as a precipitant of vasomotor symptoms (Voda, 1981). Plante and Rodin (1990), in their review of studies on exercise and psychological health, conclude that moderate exercise can improve mood and well-being by increasing levels of serotonin, dopomine and norepinephrine. It has also been suggested by Slaven and Lee (1997) that exercise may assist in the alleviation of vasomotor symptoms. Health status is also an important factor influencing depression (Avis et al, 1994; Kaufert et al, 1992; Woods & Mitchell, 1997) although it is posited by Salovey, O'Leary, Stretton, Fishkin and Drake (1991) that mood also influences judgements about health and illness. It is therefore necessary when studying the effect of HRT on mood to control for these factors.

CHAPTER 4

MEMORY

4.1 *Memory and menopause*

Memory loss, forgetfulness and foggy thinking are frequent complaints of both perimenopausal and postmenopausal women (Anderson, Hamburger, Liu, & Rebar, 1987) and are symptoms of what is referred to as a cognitive syndrome associated with oestrogen loss by Warga (1999). The study of endocrine effects on cognition, which began in the 1970s, has accumulated substantial evidence to suggest that the hormones which organise and activate brain and behavioural mechanisms for reproductive behaviour also influence brain regions involved in learning and memory across the lifespan (Sherwin, 1997)

During critical periods of central nervous system development in foetal life, oestrogen influences the sexual differentiation of tissues in specific areas of the brain. Oestrogens are involved in promoting outgrowth of neuronal processes, neuronal differentiation, and formation of synaptic connections (Toran-Allerand, 1980). The consequent differences in patterns of neuronal connectivity that develop prenatally because of differences in the hormonal milieu between the sexes may underlie some of the quantitative sex differences in specific cognitive functions that have been reliably established in adult men and women (Sherwin, 1998). For example, on average women excel in verbal abilities, in perceptual speed and accuracy, whereas men excel in spatial and quantitative abilities (Williams & Meck, 1991). This sexual dimorphism results from the organising effects of gonadal hormones which are permanent. However, gonadal hormones also have activational effects which are responsible for continuing

effects throughout the lifespan and it is likely that dysregulation or deficiency of gonadal hormones may have effects on adult human brain function (Fillit, 1994). Thus, the loss of oestrogen in mid-life women may have profound effects on brain function as it does on other organ systems. Evidence from neuroscientific animal research suggests two mechanisms by which circulating oestrogens may effect the structure and function of brain areas known to be critically involved in memory.

4.2 *Aetiology of memory loss at menopause*

Firstly, oestrogens and progestins regulate synaptogenesis in the hippocampus during the oestrous cycle of the female rat (McEwen, Alves, Bulloch & Weiland, 1997). Bilateral ovariectomy in female rats is followed by a significant decrease in dendritic spine density on CA1 pyramidal cells of the hippocampus (Gould, Woolley, Frankfurt & McEwen, 1990). Moreover, this decrease in dendritic spine density in ovariectomised animals can be prevented by the administration of oestrogen following surgery. The fact that oestrogen-concentrating cells are present in the CA1 region of the hippocampus (McEwen, Alves, Bulloch & Weiland, 1997) suggests that maintenance of dendritic spine density may be a direct effect of this sex steroid, particularly as a positive correlation between dendritic spine density and circulating oestrogen occurred in the intact female rat (Woolley, Gould, Frankfurt & McEwen, 1990). Since it is likely that changes in dendritic spine density reflect changes in synaptic density (Gould, Woolley & McEwen, 1991), it is possible, according to Sherwin (1998) to conclude that oestrogen enhances the function of the CA1 area of the hippocampus which is known to be critical for memory.

Secondly, oestrogen interacts with the cholinergic system. It increases choline acetyltransferase, the enzyme needed to synthesize the neurotransmitter acetylcholine (Luine, 1985). Cholinergic mechanisms are critically involved in attentional processes and in learning and memory (Henderson, 1997). Administration of estradiol to ovariectomised rats increases cholinergic markers in portions of the basal forebrain and other specific brain regions (Luine, 1985). Basal forebrain cholinergic neurons possess both nuclear receptors for oestrogen and low-affinity receptors for nerve growth factor. The nerve growth factor prevents atrophy of cholinergic neurons after injury and oestrogens may possess the general property of regulating or modulating the neurotrophins (Toran-Allerand, 1996).

4.3 *HRT and memory*

Despite the strong biological indications that oestrogen affects cognitive function, research into the effect of HRT on memory has produced equivocal results. However, there are strong indications from well-controlled studies, both observational and clinical trials, that oestrogen helps to maintain some aspects of short- and long-term verbal memory in women.

Several observational studies of postmenopausal women which have compared oestrogen users and non-users on a variety of memory tasks have found a beneficial effect of oestrogen. Significantly better performance has been found on immediate and delayed paragraph recall (Kampen & Sherwin, 1994), on proper name recall (Robinson, Friedman, Marcus, Tinklenberg & Yesavage, 1994), and on visual memory (Resnick, Metter & Zonderman, 1997). In a study which utilised neuroimaging and

neuropsychological assessment, Resnick, Maki, Golski, Kraut and Zonderman (1998) found better performance on both visual and verbal memory tasks. This study, using positron emission tomography (PET), also found significant differences in brain activation patterns during memory task performance between oestrogen users and non-users. Postmenopausal women who used oestrogen also performed better than non-users on a test battery that assessed perceptual speed, spatial skills, motor skills, verbal fluency, verbal memory and verbal reasoning (Kimura, 1995). A longitudinal study by Jacobs et al (1998) also found a positive association between previous oestrogen use and performance on tests of immediate and delayed verbal recall and word recall. In a recent study designed to explore the association between levels of sex hormones and cognitive performance in elderly women, Drake et al (2000) found that high oestrogen levels were associated with better delayed verbal memory and retrieval efficiency. In contrast to the Drake et al study which found no association between high oestrogen levels and better performance on verbal tests of short term attention and working memory, Carlson and Sherwin (1998) did find significant difference in performance on these tasks between oestrogen users and non-users but no differences in other verbal memory tests.

Observational studies of postmenopausal women which found no beneficial effect of oestrogen on memory include Barrett-Connor and Kritz-Silverstein (1993), Matthews, Cauley, Yaffe and Zmuda (1999), Schmidt et al (1996), and Szklo et al (1996). However, all these studies were investigating the effect of ERT on cognitive function generally and contained only one or two memory tests. Therefore, the negative findings can only reflect the lack of effect on the limited aspects of memory measured rather

than a lack of effect on other, possibly more relevant, domains of memory.

In addition to these observational studies several prospective randomised clinical trials have been carried out. Early trials produced mixed results with studies by Campbell and Whitehead (1977), Fedor-Freybergh (1977) and Hackman and Galbraith (1976) reporting a positive effect of oestrogen on memory and those by Rauramo, Lagerspetz, Engblom and Punnonen (1975) and Vanhulle and Demol (1976) reporting no effect. Methodological problems, particularly pertaining to the use of reliable and valid measures of memory and the gynaecological status of participants, contributed to the failure to produce consistent findings. More recent research on surgically menopausal women which has used reliable and valid measures of memory has produced more consistent results and demonstrated a positive effect of oestrogen on memory.

Three studies (Phillips & Sherwin, 1992; Sherwin, 1988; Sherwin & Phillips, 1990) have evaluated the role of oestrogen in women about to undergo total abdominal hysterectomy and bilateral oophorectomy. In the Sherwin (1988) trial, women were memory tested one month prior to surgery, three months after surgery following treatment with varying combinations of hormone replacement or placebo, and after a further four months following a month of placebo and crossover to a different three month treatment condition . A group of women who only underwent hysterectomy served as a control for the surgical procedure itself. Women who received oestrogen treatment maintained their pre-operative scores on the short-term verbal memory tasks (short-term attention and paragraph recall) whereas groups on placebo experienced significant declines on these tests. These results were confirmed in a similar study

(Sherwin & Phillips, 1990) which tested memory after two months of postoperative oestrogen or placebo. This study found that retention of new material was maintained in women receiving oestrogen but had decreased significantly compared to preoperative baseline in women who received a placebo. In the paragraph recall test, the scores of women receiving oestrogen increased significantly compared to preoperative baseline, while the scores of those given placebo were maintained. This study also tested immediate and delayed visual recall but no changes in scores were recorded for either group. In the third study (Phillips & Sherwin, 1992), the oestrogen-treated group performed significantly better than the placebo-treated group on immediate paragraph recall and on both immediate and delayed retention of new material. While this study confirmed the lack of hormonal effect on visual memory found in the Sherwin and Phillips (1990) study, no effects were apparent on delayed paragraph recall or verbal tests of short term attention and working memory.

This improvement in verbal memory with oestrogen replacement was also demonstrated in a study of younger women with uterine myomas. Sherwin and Tulandi (1996) found that women treated with leuprolide acetate depot (a gonadotropin-releasing hormone agonist which suppresses ovarian hormone production and results in a reduction in the volume of the oestrogen-sensitive tumors) demonstrated a significant decrease in scores on verbal memory tests, and that these deficits were reversed in women who received "add-back" oestrogen but not in those who received "add-back" placebo. Tests of both immediate and delayed paragraph recall, and immediate paired-associates recall reverted to pretreatment levels in women treated with oestrogen but remained depressed in the placebo group. Scores on the verbal tests of short term attention, working

memory, and visual memory tests did not change signifcantly in either group during the course of the study. The authors suggest that, not only do these findings demonstrate that memory deficits induced by oestrogen deprivation are reversible in the short term, but they also serve to control for possible experimental confounds, such as the surgical procedure itself, differential rates of postoperative recovery, and factors related to the ageing process, that may have influenced the results of the studies mentioned above in surgically menopausal women.

In contrast to the above research by Barbara Sherwin, three recent randomised double-blind placebo trials (Ditkoff, Crary, Cristo & Lobo, 1991; Polo-Kantola et al, 1998; Shaywitz et al, 1999) have failed to show that short-term verbal memory is improved by oestrogen replacement therapy. However, in all three trials there was no specific testing of verbal memory. Ditkoff et al (1991) and Polo-Kantola et al (1998) used only numerical tests of short-term attention and working memory; and Shaywitz et al (1999) used a computerised test of pronounceable nonsense words of unknown reliability and validity. While the Shaywitz et al (1999) study found that oestrogen did not affect actual performance on the verbal memory tasks, it did evaluate brain activation patterns using functional MRI during cognitive testing and concluded that oestrogen does affect brain organisation for memory in postmenopausal women.

4.4 *Methodological issues*

While the difference in the results of these studies may be caused by variability of study designs, including different subject inclusion criteria, failure to control for factors which may influence the relationship between memory and HRT (e.g. mood, concomitant use

of other medications), and the use of different oestrogen preparations and dosages, probably the area of greatest concern is the limited way in which memory has been defined and measured.

4.4.1 Definition of memory

Memory, the encoding, storage and retrieval of information acquired through the senses, is not a unitary system, rather an alliance of interrelated subsystems (Baddeley, 1995). There are several models of memory which emphasise various structures, processes, stages and types of storage systems and it is these models which have guided laboratory-based research, been influential in memory test development, and defined the various subsystems of memory.

Predominant among these models are those of Atkinson and Shiffrin (1968) and Tulving (1972). The Atkinson and Shiffrin model divides memory into sensory memory, short-term memory (memory for material that has just been presented and is still in conscious awareness), and long-term memory (memory for material that has left conscious awareness from seconds to years ago) and focuses on the length of time material has been in memory. The Tulving model, which focuses on the nature of the material that is stored in memory, expanded the concept of long-term memory into episodic memory (memory for specific experiences), semantic memory (memory for knowledge), and procedural memory (automatic activation).

Another concept of memory, working memory, was introduced by Baddeley in 1986. Working memory can be seen as a complementary information processing approach to

the understanding of short-term memory and is a system which allows the temporary holding and manipulation of information while other cognitive tasks are performed (Baddeley, 1995). In addition to these numerous subsystems, distinctions are made between verbal, visual and spatial memory; between retrospective and prospective memory; between recall and recognition; and between free recall and cued recall. Although this fractionation of memory has given greater understanding of the larger construct, there is also the disadvantage that any one of these subsystems may simply be referred to in terms of the larger construct. This is demonstrated in many studies that draw conclusions about the effect of oestrogen on memory generally from the results of one or two neuropsychological tests which measure only specific subsystems.

Laboratory-based research based on the above models and subsystems of memory have dominated the study of memory but, since the 1970s the concept of everyday memory has emerged as an alternative approach. The emergence of this concept resulted from arguments against the narrowness of laboratory-based research and the problems of relating performance elicited in the artificial testing environment of the laboratory to natural functioning. Neisser (1978) forcefully criticised the sterility of memory research conducted in the laboratory arguing that it failed to represent memory as it occurred in the real world. Everyday memory can therefore be seen as a concept which refers to how memory is studied: as a way to introduce ecological validity into memory research by taking it outside the laboratory and into the 'real' world to gain understanding of practical functioning in everyday life tasks under realistic everyday conditions.

While there does not appear to be a standard definition for everyday memory, the term

generally refers to the memory capacities needed to manage the day-to-day living environment of the individual. It has been described as a relatively stable skill during adulthood (Youngjohn & Crook, 1993), and van Balen, Westzaan and Mulder (1996) likened it to a 'species-wide capacity'. Everyday memory calls on a combination of short-term, working, and long-term memory capacity and, particularly when applied to older people, is concerned with the maintenance rather than the extension of memory function.

While proponents of everyday memory criticise laboratory-based research for its lack of ecological validity (eg Neisser, 1978) and opponents criticise everyday memory for its lack of generalisability and control (Banaji & Crowder, 1989), there is now a wide acceptance that it is both possible and necessary to study memory outside the laboratory (de Wall, Wilson, & Baddeley, 1994). In addition there is also acceptance that everyday memory can be studied objectively and effectively by the adaptation of methods and techniques originally developed in the laboratory (Baddeley, 1990; Gruneberg, Morris, & Sykes, 1988).

4.4.2 Measurement of memory

It has been suggested by Warga (1999) that a more comprehensive approach to cognitive testing of mid-life women be adopted, one which encompasses the complaints that these women experience. Within the domain of memory such complaints include forgetting names; forgetting or not recognising faces; forgetting appointments, events, or jobs to be done; and forgetting information just heard. She claims that unless comprehensive testing of all these domains of memory is carried out using

psychometric instruments that are sufficiently sensitive to the subtle but internally evident changes that many mid-life women experience, then studies cannot conclude that oestrogen therapy has no effect of this aspect of cognition.

The memory complaints listed by Warga (1999) are all concerned with everyday memory problems, problems which are encountered in day to day living which may impinge on functioning to a greater or lesser extent. However, with the exception of the Robinson et al (1994) study which found that oestrogen use was associated with enhanced recall of proper names, research to date has used laboratory tests of memory. Not only do these tests tend to focus on how memory works rather than how individuals use the memory capacity they possess (Makatura, Lam, Leahy, Castillo, & Kalpakjian, 1999), they fail to tap into some everyday problems and therefore cannot generalise to effects on everyday functioning. Areas such as remembering people (Behrick, 1984), remembering to do things (Harris, 1984), and remembering to do things without being reminded (Wilkins & Baddeley, 1978) are notable omissions.

In view of the fact that research to date has produced equivocal results, it would be useful to focus on everyday memory. This focus would take into account the problems that mid-life women experience using instruments that are representative of such problems in that the material and items used are analogous to the situations encountered in everyday life.

4.4.3 Memory and age

While research into the effect of HRT on memory in midlife women emphasises the

effects that the decreased level of oestrogen may have on cognition, it is important to remember that the ageing process itself may account for some cognitive decline independent of any hormonal effect. Age-related decline in memory has been attributed to a number of factors including neuronal loss in the brain, inefficient use of cognitive strategies (Botwinick, 1967), lack of practice in performing cognitive tasks, and decreased motivation (Burkhill & Schaie, 1975). There is considerable evidence from laboratory studies of age differences in memory that performance on memory tasks declines with increasing age (Craik, 1977). However, age differences in performance depend on the specific aspect of memory being tested.

In short-term memory, performance on immediate or primary memory tasks which do not require storage and retrieval of material, such as digit span tasks, show virtually no change with age (Parkinson, 1982). However, on tasks that require working memory in which information must be held while some decision-making activity is carried out on the information, there are decreases in both speed and accuracy with normal ageing (Wingfield, Stine, Lahar & Aberdeen, 1988). In long-term memory, performance on tasks related to episodic memory generally declines with age although the degree of impairment seems to depend on the availability of environmental cues. It has been found that age-related decrements are reduced to the extent that instructions or orienting tasks are given at the time of acquisition and supportive conditions (e.g. cued recall or recognition) are given at the time of retrieval (Craik, Anderson, Kerr & Li, 1995). Semantic memory performance shows less decline across the adult life-span than episodic memory (Light, 1992) although age-related decrements in retrieval of semantic knowledge have been found (Bowles & Poon, 1985). Procedural memory is least

affected by ageing although skills of a discontinuous nature, in which a series of discrete stimulus-response links are involved, such as typing, are prone to forgetting when not used (Baddeley, 1995). While this research relates mainly to verbal retrospective memory, visual, spatial and prospective memory also show age-related decline when environmental cues are not available and strongly indicate that for all long-term memory performance age differences are greatest in free recall, less in cued recall and least in recognition (Craik, Anderson, Kerr & Li, 1995).

Because none of the above research on memory and ageing assessed sex differences or measured hormone levels, it is not possible to assess the extent to which these factors contribute to cognitive abilities in healthy older people (Sherwin, 1997). However, it does point to the necessity of controlling for age when investigating the effects of HRT on memory.

4.4.4 Memory-inhibiting drugs

It is also necessary to control for concomitant medications as a number of drugs have been shown to interfere with memory functioning. Benziazepines, including diazepam and triazolam, have been demonstrated to induce impairments in performance on many types of memory tests, including recall and recognition tests. This class of drugs acts primarily by facilitating the activity of the neurotransmitter GABA, although the activities of other types of neurotransmitters are also altered (Curran, 1991). Drugs with anticholinergic action have also been demonstrated to interfere with performance on some memory tests. These drugs interfere with the action of the neurotransmitter acetylcholine. Scopolamine, a muscarinic cholinergic receptor antagonist, has been

shown to interfere with both recall and recognition performance (Beatty, Butters & Janowsky, 1986).

4.4.5 Memory and mood

It is well established that negative mood states are frequently associated with impairment of memory and other cognitive functions (Deptula, Manevitz, & Yozawitz, 1991). A prominent explanation for such memory impairment is the resource allocation model of Ellis and Ashbrook (1988) which assumes that a negative mood state will reduce the likelihood that a person will allocate or deploy attentional resources to a memory task. This occurs because the emotional state leads to an increase in irrelevant thoughts that compete with relevant cognitive activities important for memory. These intrusive, irrelevant thoughts pre-empt allocation of attention to the memory task, and thus impair performance. It has also been found that ageing moderates the relationship between emotional state and memory functions in that older people are more vulnerable than the young to the adverse effects of negative emotional states on memory (Deptula, Singh, & Pomara, 1993). It is therefore suggested by Sherwin (1997) that mood be assessed at the same time that neuropsychological functions are investigated, to control for the possibility that any enhancement of memory by oestrogen therapy may occur secondary to its enhancement of mood.

The majority of studies that have investigated the effect of HRT on memory have not assessed mood and have therefore been unable to assess this secondary effect on memory. Of those which have controlled for mood, several have found no effect of HRT on mood in the presence of enhanced memory (Drake et al, 2000; Jacobs et al,

1998; Kimura, 1995; Phillips & Sherwin, 1992; Robinson et al, 1994; Sherwin & Phillips, 1990). Conversely, Ditkoff et al (1991) found enhanced mood with HRT but no change in performance on memory tasks. Given the neuroscientific evidence of the impact of oestrogen on both mood and memory, and the established relationship between mood and memory, it is highly likely that the previously mentioned methodological issues, which culminate in this research, have prevented this secondary effect of oestrogen on memory being demonstrated in the above studies.

CHAPTER 5

SUMMARY

There is considerable neuro-scientific evidence that oestrogen enhances mood and influences memory because of its influence on brain mechanisms. This evidence suggests oestrogen influences mood by altering the concentrations and availability of neurotransmitter amines, including serotonin (Halbreich, 1997), and influences cognitive functions associated with memory through its actions on brain structures such as the hippocampus and basal forebrain (McEwen, Alves, Bulloch & Weiland, 1997).

While menopause has been associated with disturbances of mood and behaviour by medical observers since the 18th century, research has failed to systematically link major depressive disorder with changes in hormonal status (Schmidt & Rubinow, 1991). However, there are indications that, for a minority of women, there may be a modest increase in depressive symptoms during perimenopause (Avis, Brambilla, & McKinlay, 1994). Although, overall, research on the effect of hormone replacement therapy is equivocal, placebo-controlled trials of oestrogen replacement in naturally menopausal women without significant baseline depressive symptomology indicate a beneficial effect on mood and sense of wellbeing (Pearlstein, Rosen & Stone, 1997).

Research which has looked at the effect of hormone replacement on memory is also equivocal in its conclusions. However, there are strong indications from experimental research which involved assessment of cognitive functions in premenopausal women before they underwent surgical menopause and then repeated assessment

postoperatively during treatment with oestrogen or placebo, that oestrogen serves to maintain or enhance verbal memory in women (Sherwin, 1997).

It is well established that negative mood states are frequently associated with impairment of memory and other cognitive functions (Deptula, Manevitz & Yozawitz, 1991). It has also been found that ageing moderates the relationship between emotional states and memory functions in that older people are more vulnerable than the young to the adverse effects of negative emotional states on memory (Deptula, Singh & Pomara, 1993). This relationship between mood and memory suggests the importance of assessing mood at the same time that neuropsychological functions are investigated. Such assessment would allow for control of the possibility that the enhancement of memory by oestrogen may occur secondary to its enhancement of mood.

Studies which have investigated the relationship between oestrogen replacement therapy, mood and memory have produced confusing results and it is suggested that this is because of the way in which the constructs of mood and memory have been defined and/or measured. Mood may be defined in terms of normal, elated or depressed states and people experience a wide range of mood states. However, in this body of research mood has most frequently been defined in terms of depression or depressed mood with little attention being paid to positive affect or other less clinical mood states which occur in the everyday lives of normally functioning mid-life women. While the research has not treated memory as a unitary system and has examined the effect of oestrogen on well-defined areas of the construct, measurement has been largely restricted to laboratory-type testing which has been criticised for its lack of salience to

the research participant. As Conway (1991) suggests, most experimental-type tasks are meaningless to participants as the material to be remembered is difficult to process in any self-relevant way. As mid-life women complain about everyday problems, such as forgetting names, appointments, and information just heard, it would appear more relevant to measure these aspects of everyday memory in order to achieve greater ecological validity.

In view of the equivocal nature of the research which has investigated the effect of oestrogen on memory and mood, the present study will examine the effect of hormone replacement therapy on a broad spectrum of mood states and everyday memory and investigate the possible mediating effect of the various mood states on the relationship between oestrogen and everyday memory.

CHAPTER 6

THE CURRENT RESEARCH

6.1 *Aim:*

The aim of the current research is to investigate the effect of HRT on mood and everyday memory in mid-life women. It will also examine the possible mediating effect of the various mood states on the relationship between HRT and everyday memory.

Despite the considerable neuroscientific evidence that supports the influence of exogenous oestrogen on cognitive functions associated with memory, research to date has produced equivocal results. It is suggested that this is largely due to the ways in which the constructs of mood and memory have been defined and measured. Mood has generally been defined only in terms of negative affect with a strong emphasis on depression. This study will therefore examine a wide range of mood states which will include both positive and negative affect, using instruments which are sensitive to mood change over time. Laboratory-based memory testing has dominated the HRT/memory research and yet this type of testing does not target the specific memory complaints that mid-life women experience. This study will therefore adopt the concept of everyday memory using an instrument that is analogous to the situations encountered in everyday life.

6.2 *Hypotheses:*

1. **HRT use will be associated with increased positive affect, decreased negative affect, and improvement in mood states, while accounting for the effects of stressful life events, self-rated health, sleep, vasomotor symptoms, and exercise among perimenopausal and postmenopausal women.**

There is evidence from placebo-controlled trials that HRT enhances mood in mid-life women (eg Klaiber et al, 1997). Research has demonstrated that stressful life events (Kaufert et al, 1992), health complaints (Avis et al., 1994) and sleep deprivation (Stone & Pearlstein, 1994) can have a negative impact on mood. It has also been found that exercise positively affects depression, anxiety, self-esteem and general mood (Slaven & Lee, 1997). This hypothesis will test the psychosocial theory (McKinlay et al, 1987) that mood changes in menopause occur in response to stressful life events and health problems which may coincide with the menopause transition and cause women to be particularly vulnerable to depression at this time. It will also test the domino theory (Dennerstein & Van Hall, 1986) which suggests that menopausal mood changes arise from the somatic symptoms that appear due to oestrogen decline: that dysphoria which may occur during the menopause transition is secondary to vasomotor symptoms.

2. HRT use will be associated with improved short-term attention, short-term working memory, everyday memory, and verbal memory while accounting for the effects of age, IQ, education and memory-affecting medications, among peri-menopausal and post-menopausal women.

Based on the biological evidence of the neurosciences that oestrogen influences areas of

the brain known to be important in memory and learning, and evidence from research which suggests that verbal memory is enhanced by oestrogen therapy in postmenopausal women (Phillips & Sherwin, 1992) when laboratory-type memory testing is used, it is hypothesised that everyday memory will improve with HRT use. Education has been found to protect against cognitive decline in postmenopausal women (Matthews, Cauley, Yaffe & Zmuda, 1999). There is considerable evidence from laboratory studies of age differences in memory that performance on memory tasks declines with increasing age (Craik, 1977). Drugs with anticholinergic action, and benziazepines are known to interfere with memory functioning and their use as concomitant medications must be controlled for.

3. The relationship between memory and HRT use will be mediated by mood.

The strong evidence that negative mood states are associated with the impairment of memory (Deptula, Manevitz, & Yozawitz, 1991) suggests that any improvement of memory may be secondary to an improvement in mood states.

CHAPTER 7

METHOD

7.1 *Study design*

In order to investigate the short-term effects of HRT on mood and everyday memory and examine the differences in measures of mood and everyday memory between HRT users and non-users two study designs were used: longitudinal and cross-sectional. The longitudinal aspect of the study investigated the short-term effect of HRT on mood states and everyday memory performance and involved women who were about to start using HRT. These women were interviewed before they started using HRT and again after 3 months if they were still using HRT: a longitudinal, quasi-experimental, within-subject design. The cross-sectional aspect of the study investigated the differences in mood states and everyday memory performance between a group of women who were using HRT and a group of women not using HRT: a cross-sectional, between-subject, correlational design.

7.2 *Participants*

To meet the requirements of the two study designs, two samples of participants were obtained. The samples were mutually exclusive. Participants for both samples were women between the ages of 39 and 60 years (inclusive). The women were invited into the study by their general practitioner or through a press release in provincial newspapers (see Appendix 1). As the average age at menopause is 51 years but perimenopause may precede the final menses by between 2 and 8 years and symptoms of menopause may continue for several years after menopause (Greendale, Lee, & Arriola, 1999), the age group was selected to include women for whom HRT may be

prescribed to alleviate the symptoms of menopause. Within these parameters all women, regardless of HRT use status, were eligible for inclusion into either the cross-sectional sample or the longitudinal sample. Participation was voluntary.

The cross-sectional sample consisted of women who were already using HRT (HRT users) and those who were not using HRT (non-users). A total of 124 women were interviewed: 62 (50%) in the HRT group and 62 (50%) in the non-HRT group. The majority (75%) of these participants were recruited through the press. The age range for this sample was 41-60 years with a mean of 51.6 years. Table 1 shows the demographic data for this sample.

Table 1
Demographic data for cross-sectional and longitudinal samples.

	Cross-sectional sample (n – 124)		Longitudinal sample (n – 18)	
Age (mean in years)	51.4		49.0	
	n	%	n	%
Ethnicity				
NZ European	110	(88.7)	18	(100)
NZ Maori	4	(3.2)	-	-
European	10	(8.1)	-	-
Education				
Less than 11 years	30	(24.2)	4	(22.2)
11-13 years	43	(34.7)	7	(38.9)
More than 11 years	51	(41.1)	7	(38.9)
Employment				
Full-time paid	61	(49.2)	11	(61.1)
Part-time paid	39	(31.5)	5	(27.8)
Self-employed	4	(3.2)	-	-
Not in paid employment	20	(16.1)	2	(11.2)

The longitudinal sample consisted of women who were about to start taking HRT. Eighteen women were interviewed before they started taking HRT and again after completing three months of treatment. The majority (86.7%) of these participants were recruited through medical practitioners. The age range for this sample was 39-59 years with a mean of 49 years. Table 1 shows the demographic data for this sample.

7.3 *Measures*

7.3.1. Measurement of memory

The Rivermead Behavioural Memory Test – Extended Version (RBMT-E)

The original version of this test, the Rivermead Behavioural Memory Test (Wilson, Cockburn & Baddeley, 1985) is essentially an atheoretic test designed to detect impairment in everyday memory function and monitor treatment in people with acquired, non-progressive brain injury. The RBMT-E (Wilson et al, 1999) is a longer and more demanding version of the RMBT which detects mild deficits and change in everyday memory within a normal adult population. It consists of 11 subtests (see Appendix 3) which can be seen to measure different aspects of memory: long and short term; recall and recognition, visual, verbal, prospective, procedural, and semantic memory. These subtests assess everyday skills: recall of names; recall and whereabouts of belongings; cued remembering of questions related to appointments; immediate and delayed recall of a story and a route traced around a room; recognition of faces and pictures; orientation of time and place; and knowledge of political leaders and the date. There are two parallel versions of the test (Wilson et al, 1999).

The RBMT-E was designed to follow the original RBMT structure and is therefore assumed to have the same established validity and sensitivity (Wilson et al, 1999). Research within New Zealand using the RBMT by Fraser, Glass and Leathem (1999) confirmed the excellent face validity and recognised ecological validity of the test. It also has high alternate-form reliability between the two versions of the test. Mean scores are available for normal populations based on age, gender and IQ levels (Wilson et al, 1999) and comparable scores were found in a pilot study carried out to test the suitability of this measure on New Zealand women (see Appendix 4).

Administration of this test was carried out by the researcher. Instructions to the participants were printed verbatim in books of Test Materials for each version of the test and were strictly adhered to in all testing. All scoring was carried out by the researcher in accordance with the RBMT-E Manual (Wilson et al, 1999). The 11 subtests produced 12 raw scores which were summed to produce a total raw score. The total raw score had a possible range of 0-157; a high score indicating good everyday memory. Table 2 shows the possible range and present sample range of RBMT-E sub-tests and total raw score for the cross-sectional and longitudinal samples. Although the raw scores can be converted to profile scores (which control for age, IQ level and test version) for diagnostic purposes, raw scores were used for analysis in this research to prevent the loss of detailed information on the individual subtests. In this study the alpha coefficient was .63 (n = 124). This low internal reliability reflects the heterogeneous nature of the test in that it measures several different aspects of memory within the one test.

While the total raw score of the RBMT-E was to be used as a measure of overall everyday memory, the subtests of 'Story Immediate' and 'Story Delayed' were used as measures of verbal memory. These subtests require that the subject listen to a short paragraph of prose being read out and then recall as much of it as possible immediately, and then again after approximately 20 minutes (during which time other subtests are carried out) and are equivalent to the verbal memory tests used in the Sherwin (1988, 1990) research.

Table 2
Possible range and present sample range of the Rivermead Behavioural Memory Test – Extended Version (RBMT-E) sub-tests and total raw score for cross-sectional and longitudinal samples.

	Possible range	Cross-sectional sample range	Longitudinal sample range
First names	0-6	1-6	1-6
Second names	0-6	0-6	0-6
Belongings/Appointments	0-12	0-12	4-12
Picture recognition	0-20	7-20	1-19
Story (immediate)	0-21	1-17	1-16
Story (delayed)	0-21	0-15	1-17
Face recognition	0-15	5-15	10-15
Route (immediate)	0-15	5-15	7-15
Route (delayed)	0-15	6-15	5-15
Messages (immediate)	0-6	3-6	4-6
Messages (delayed)	0-6	2-6	4-6
Orientation and date	0-14	11-14	12-14
Total score	0-157	75-136	85-142

Digit Span

Digit Span is an optional subtest on theWechsler Memory Scale – Third Edition (WMS-III; Wechsler, 1997). This measure is composed of Digit Span Forward and Digit Span Backward, which are thought to tap into different short-term memory functions (Lezak, 1995). Digit Span Forward is a measure of focused attention whereas Digit Span Backward, while also measuring focused attention, demands more effort from working memory. Digit Span was used in this study to provide a specific assessment of short-term attention and short-term working memory as, although these aspects of memory are incorporated into the RBMT-E, they are not specifically measured.

Digit Span has test-retest reliability of .83 and split-half internal consistency of .91 for the 45-54 age group. It has good criterion-related and construct validity with WAIS-R (Wechsler Adult Intelligence Scale – Revised) and WISC-III (Wechsler Intelligence Scale for Children – Third Edition; Wechsler, 1997).

On both tasks, the researcher read a series of number sequences to the participant (see Appendix 3). For each Digits Forward item, the participant was required to repeat the number sequence in the same order as presented. For Digits Backwards, the participant was required to repeat the number sequence in the reverse order. Each subtest was discontinued when the participant scored 0 on both trials of an item. A score for each subtest was achieved by summing the number of correct answers; a high score indicating good Digit Span memory. The range of possible scores was: Digit Span Forward 0-16, Digit Span Backward 0-14. The range for the cross-sectional sample was: Digit Span Forward 6-16, Digit Span Backward 2-14. The range for the

longitudinal sample was: Digit Span Forward 1-15, Digit Span Backward 2-13. respectively.

7.3.2 Measurement of mood

Two standardised, reliable and valid psychometric measures of different aspects of mood were used: the Positive and Negative Affect Schedule (Watson, Clark & Tellegen, 1988 and the Profile of Mood States (McNair, Lorr & Droppleman, 1981). These measures were combined (see Appendix 3) and administered as a written questionnaire.

Positive and Negative Affect Schedule (PANAS)

PANAS (Watson, Clark & Tellegen, 1988) was designed to measure two dominant and relatively independent dimensions of affective structure – positive affect (PA) and negative affect (NA). PA reflects the extent to which a person feels enthusiastic, active and alert. High PA is a state of high energy, full concentration and pleasurable engagement, whereas low PA is characterised by sadness and lethargy. In contrast, NA is a general dimension of subjective distress and unpleasurable engagement that subsumes a variety of aversive mood states, including anger, contempt, disgust, guilt, fear and nervousness, with low NA being a state of calmness and serenity (Watson et al, 1988).

The two 10-item 5-point adjective rating scales have demonstrated high internal consistency with alpha reliabilities ranging from .86 to .90 for PA and from .84 to .87 for NA; the reliability of the scales is stable over a 2-month time period. The scales are

largely uncorrelated (-.12 to -.23), have adequate test-retest reliability, high convergent validity, and excellent factorial validity (Watson et al, 1988).

In the present study, participants were asked to rate on a 5-point scale the extent to which they had experienced each mood state during the past week. Total scores for PA and NA were calculated by summing the responses for the adjectives defining each scale. The range of possible scores for each scale was 10-50: a low score represented a low level of that mood dimension. For PA, the cross-sectional range was 13-48 and for the longitudinal sample it was 16-50. The alpha coefficient was .86 (n = 124). For NA, the cross-sectional range was 10-40 and for the longitudinal sample it was 10-38. The alpha coefficient was also .86 (n = 124).

Profile of Mood States (POMS)

POMS (McNair, Lorr & Droppleman, 1981) was designed to identify and assess transient, fluctuating affective states. It measures mood changes on seven affective states: Tension/Anxiety, Depression/Dejection, Anger/Hostility, Vigour/Activity, Fatigue/Inertia, Confusion/ Bewilderment and Friendliness. This measure has been recommended as a mood research tool for normal participants over the age of 18 who have had at least some high school education (McNair et al, 1981).

This 65 item 5-point adjective rating scale has shown high internal consistency with alpha reliabilities ranging from .84 for Confusion/Bewilderment to .95 for Depression/Dejection. For a mood scale it has shown high test-retest reliability ranging from .65 for Vigour/Activity to .74 for Depression/Dejection. Good factorial validity

has been demonstrated for all affective states except Friendliness and evidence of predictive and construct validity of the measure has been demonstrated in four areas of research (McNair et al, 1981).

In the present study, participants were asked to rate on a 5-point scale the extent to which they had experienced each mood state during the past week. Scores for each mood factor were calculated by summing the responses for the adjectives defining each scale: a high score reflecting a more negative mood. Two items received negative weights in calculating the factor scores. A Total Mood Disturbance Score was obtained by summing the scores (with Vigour weighted negatively) on the six primary mood factors (Friendliness excluded). The range of possible scores varied depending on the number of adjectives defining the factor. The ranges and alpha coefficients (derived from the cross-sectional sample scores) for the present study are shown in Table 3.

Table 3
Possible range, present sample ranges, and alpha coefficients of the Profile of Mood States (POMS) subscales and total mood disturbance score.

	Possible range	Cross-sectional sample range	Longitudinal sample range	Alpha coefficient (n = 124)
Anxiety	0-36	0-31	0-21	.86
Depression	0-60	0-42	0-11	.91
Anger	0-48	0-33	0-18	.86
Fatigue	0-28	0-25	0-23	.89
Confused	0-28	0-22	0-18	.82
Vigour	0-32	1-32	4-28	.90
Friendly	0-28	7-28	9-27	.79
Total MDS	0-260	7-151	11-88	.85

7.3.3 Measurement of possible confounding variables

Vasomotor symptoms and sleep problems

The Women's Health Questionnaire (WHQ, Hunter, 1992) was administered to measure quality of life during menopause with particular regard to vasomotor symptoms and sleep problems. This measure was designed specifically to study possible changes in health and well-being during the menopause transition (see Appendix 3). It is a measure of mid-aged women's perceptions of their emotional and physical health which has been found to be a sensitive measure of response to hormone replacement therapy (Wiklund et al, 1992). Test-retest reliability across a two-week time interval for the 9 subscales has been reported as ranging from .69-.96 (Hunter, 1992). Alpha coefficients ranging from .62-.82 have been reported on 6 of the subscales (Wiklund et al, 1992). This measure has high face validity, and concurrent validity for the depressed mood scale has been confirmed by comparison with the 30-item General Health Questionnaire (Goldberg, 1972) which measures mood disturbance in community samples (Hunter, 1992).

In the present study, this 36-item self-administered measure asked participants to respond to statements about how they had been feeling during the past week on a 4-point rating scale and produced 9 subscales: Depression, Anxiety/fears, Memory/concentration, Sleep problems, Somatic symptoms, Vasomotor symptoms, Sexual behaviour, Menstrual symptoms and Attractiveness. Scores for each subscale were obtained by summing the scores for each item (6 items were reverse scored) pertaining to a particular subscale and dividing that score by the number of items in the subscale. This produced a range of possible scores of 0-3 for each subscale with a high

score reflecting greater symptom experience or more difficulties in a particular area. The subscales were added to produce an overall measure of well-being with a range of 0-3: a high score indicating a lower level of well-being. The sample ranges and alpha coefficients (derived from the cross-sectional sample scores) for the present study are shown in Table 4. The extremely low internal reliability of the Attractiveness subscale reflects the fact that this subscale comprised only two items and one of these ("I feel rather lively and excitable") was ambiguous to many participants. While 'liveliness' was construed as a positive characteristic, 'excitability' was not.

Table 4
Sample ranges and alpha coefficients of the Women's Health Questionnaire (WHQ) subscales and total wellbeing score.

WHQ	Cross-sectional sample range	Longitudinal sample range	Alpha coefficient (n = 124)
Depression	0-2.29	0-1.86	.72
Anxiety	0-2.50	0-2.50	.75
Somatic problems	0-2.57	.14-2.57	.66
Memory problems	0-3.00	.22-3.00	.72
Vasomotor symptoms	0-3.00	0-3.00	.86
Sexual difficulties	0-3.00	0-2.67	.65
Sleep disturbance	0-3.00	0-2.67	.59
Menstrual problems	0-2.75	0-2.50	.64
Attractiveness	0-3.00	0-2.50	.30
Total wellbeing score	.19-1.97	.15-2.49	.78

Stressful life events

A brief measure of stressful life events was adapted from Norbeck's (1984) Life Event Questionnaire. This 7 item measure (see Appendix 3) asked participants to think about stressful events which had happened in different areas of their lives over the past year

and rate the level of stress experienced on a four-point scale. The areas of stressful events included family, close friends, love and relationships, work, financial, and being a victim of crime. This measure was designed specifically for adult females and has good face validity. Test-retest reliability over a two-week interval on 10 mid-life women was .87 ($p<.01$). A total stress score was calculated by adding the scores on all items which produced a possible range of 0-21: a low score represented low stress. The range for the cross-sectional sample was 0-17 with a mean of 7.98 (SD 3.99); for the longitudinal sample it was 2-14 with a mean of 9.22 (SD 2.96).

Self-assessed health status

A measure of perceived health was used which asked participants to rate their health over the past 12 months on a five-point scale. This measure has been found to be a significant predictor of mortality in older adults (Wolinsky & Johnson, 1992). The scale ranged from very good to very poor with a high score indicating a perception of good health. In this study, 77.4% of the cross-section sample and 83.3% of the longitudinal sample rated their health as good or very good.

Exercise

Using a yes/no response format, moderate exercise was assessed as exercising for at least 30 minutes, at least 3 times a week. This measure was adapted from Blalock et al (1996) who report that past research using similar measures supports the validity of self-reported assessments of physical activity and exercise behaviour. In this study, 74.2% of the cross-sectional sample and 72.2% of the longitudinal sample undertook regular exercise

IQ levels

The National Adult Reading Test (NART; Nelson, 1982) was administered to estimate IQ levels. This test was specifically designed to provide a means of estimating the premorbid intelligence levels of adult patients suspected of suffering from intellectual deterioration. The test comprised a list of 50 words printed in order of increasing difficulty. The words were all 'irregular' with respect to the common rules of pronunciation in order to minimise the possibility of reading by phonetic decoding rather than word recognition.

Nelson (1982) reported a split half reliability for the NART of .93. Inter-rater reliabilities of .96 to.98 and test-retest reliability of .98 have also been reported (O'Carroll, 1987; Crawford, Parker, Stewart, Besson & de Lacey, 1989). Cross validation research confirms the validity of the NART as a measure of general intelligence in the normal adult population (Nelson & Willison, 1991).

In this study participants were presented with a notebook which contained one word from the printed list on each page. They were asked to turn each page in their own time and read aloud the word presented. Participants were warned that there were many words that they would not recognise and were asked to have a guess at those words. A tape recording of the list of words was compiled by Dr Nancy Pachana (School of Psychology at Massey University) which contained the correct pronounciation(s) of each word in order to standardise the scoring procedure for the researchers. Using a score sheet (see Appendix 3) the number of errors made was recorded. Wechsler Adult Intelligence Scale (WAIS) Full-Scale IQs can be predicted from this error score by

inserting it into the appropriate formulae (Nelson & Willison, 1991). In the cross-sectional sample, IQ levels ranged from 80-131 with a mean of 111.76 (SD 10.63). In the longitudinal sample, IQ levels ranged from 82-128 with a mean of 111.67 (SD 11.84).

7.3.4 Measurement of demographic information

Demographic information (see Table 1 and Appendix 3) obtained included age, ethnicity, education and employment status. Data was also collected on participants' history of smoking; diseases such as diabetes, high blood pressure, heart disease, epilepsy, cancer, depression, and pre-menstrual tension; and family history of neurological conditions. Participants were asked about gynaecological surgery they had undergone (hysterectomy or ovarian) to determine natural or surgical menopause, and their menopausal status (perimenopausal or postmenopausal) was assessed from questions about their recent menstrual cycle. Perimenopause was assumed when irregularity of the menstrual cycle and/or vasomotor symptoms were reported. Post-menopause was assumed when no menstrual period over the last twelve months was reported.

Information was also sought about whether or not participants were taking any form of hormone replacement medication and about any other medication they were currently taking. HRT was coded according to method of administration and regimen. All other medications were coded according to therapeutic classification after a check in *New Ethicals (2000)* as to whether or not each medication contained drugs which are known to affect memory.

7.4 *Procedure*

It was initially planned to recruit all participants through general medical practitioners. Because HRT is a prescription drug this was deemed the most direct way in which to recruit women who were experiencing menopausal problems. General practitioners and gynaecologists throughout New Zealand were invited to collaborate through advertisements placed in GP Pulse (21.4.99) and NZ Family Physician (23.6.99). Multicentre ethical approval for the research was obtained from Manawatu/Whanganui (Lead), Auckland, Bay of Plenty, Canterbury, and Otago Ethics Committees as these were the areas in which medical practitioners agreed to collaborate. Ethical approval was also granted by the Massey University Human Ethics Committee. For logistical reasons, the Otago area could not be included in the study. A research assistant was employed to collect data in the Canterbury area. The research assistant was trained in the interview and memory testing protocol by the researcher.

Medical practitioners who expressed an interest in collaboration were sent a copy of the Health Professional Information Sheet (see Appendix 2) and visited by the researcher to discuss the study. Envelopes entitled "Menopause, Mood & Memory" were left with each practitioner who was willing to collaborate. The role of the practitioner was to introduce the study to women patients who met the research criteria. The practitioners were requested to hand an envelope to those who expressed an interest in participation. The envelopes contained a participant Information Sheet (see Appendix 2), Reply Form (see Appendix 2) and a free-post envelope.

As the number of women recruited under this protocol was low (n = 35), approval was obtained from the Massey University Human Ethics Committee to recruit participants from the community through a press release (see Appendix 1). Under this protocol, women who responded to the press release were sent a revised Information Sheet (see appendix 2), Reply Form (see Appendix 2) and a free-post envelope by the researcher.

Women who were interested in participation after reading the Information Sheet were requested to complete the Reply Form and return it to the researcher in the free-post envelope provided. On receipt of the Reply Form, the researcher contacted the respondent by telephone, confirmed a willingness to participate, and arranged a time for interview and memory testing which was convenient to the participant. Interviews were conducted in the participants' homes. Women who were eligible for the longitudinal aspect (about to start taking HRT) of the study were interviewed twice, once before they started HRT and again after 3 months of taking HRT. Contact for the second interview was made directly by the researcher (or research assistant in the Canterbury area). Women in this category who discontinued their HRT prescription within 3 months were not reinterviewed and their first interview data was transferred to the cross-sectional study. Those eligible for the cross-sectional study (using or not using HRT) were interviewed only once.

7.4.1 Interview Protocol

All interviews were conducted in the homes of the participants. The interview and testing procedures were briefly explained and informed consent was obtained through the presentation of the Consent Form (see Appendix 2) which the participant was

requested to read and sign. The interview time was approximately one hour and the interview protocol was identical for all participants. Participants in the longitudinal study repeated the same protocol after three months; the only difference being that alternate forms of the Rivermead Behavioural Memory Test – Extended Version were used for each test.

After the Consent Form was signed the demographic questionnaire was administered by the researcher. The mood measures questionnaire was then completed by the participant during which time the researcher planned the route to be traced around the room for the RBMT-E route sub-tests. The Digit Span tests, RBMT-E, and NART were then administered by the researcher and finally the WHQ questionnaire was completed by the participant. Participants completed each section of the interview protocol in their own time, the only time limitation involved was a 20 minute interval between the immediate and delayed story and route sub-tests of the RBMT-E which was incorporated into the design of that measure.

7.5 *Statistical analysis*

Statistical analysis was completed using SPSS for Windows, Release 9.0.1 (1999). Means and standard deviations were computed for each of the continuous variables measured. Pearson's r correlations were used to examine relationships between variables.

Analysis of the cross-sectional sample data involved the use of chi-square tests and independent t-tests to detect differences between the groups. Hierarchical multiple

regression was used for hypothesis testing.

Analysis of the longitudinal sample data involved the use of binomial sign tests and repeated measures t-tests to assess change over time. Two-way mixed design ANOVA was used for hypothesis testing.

CHAPTER 8

RESULTS

8.1 *Data management*

The data was screened for accuracy and missing data. Accuracy was checked by random selection of questionnaires for confirmation of correct data entry and frequencies were examined to check for out of range values and missing data. There were no missing data.

One participant in the longitudinal sample was identified as a multivariate outlier on all the mood variables between pre-HRT and post-HRT and was removed from the analysis (n = 17).

In order to test the hypotheses for the longitudinal sample, change variables were computed for the potentially confounding variables: stressful life events, self-rated health, sleep problems, vasomotor symptoms, positive affect, negative affect, total mood disturbance (POMS), and the POMS subscales. These change variables, which were the differences in scores between pre-HRT and post-HRT interviews, were between-subject variables to be used as covariates to examine whether the change on these variables between pre-HRT and post-HRT was having an effect on the dependent variables. Change variables were also computed for the memory variables to investigate the relationship between mood and memory.

Normality of distribution was examined using normal probability plots and the calculation of skewness and kurtosis statistics on all continuous variables of

hypothetical interest. The Negative Affect, Anxiety, Depression, and Anger variables in the cross-sectional sample were positively skewed and logarithmic transformations were conducted on these variables to achieve normal distributions and meet the assumptions of parametric statistical tests.

8.2 *Descriptive statistics*

Cross-sectional sample

Chi square tests for independence or relatedness were conducted to test for differences between the HRT users group and the non-user group on the nominal level variables. As some of the variables did not meet the assumption of size of expected frequencies it was not possible to detect differences between the groups on these variables.

Table 5
Demographic data for HRT user and non-user groups showing number of participants and percentage in each group.

	HRT users (n = 62)		Non-users (n = 62)	
Ethnicity				
NZ European	56	(90.3)	54	(87.1)
NZ Maori	0	-	4	(6.5) #
European	6	(9.7)	4	(6.5)
Education				
Less than 11 years	15	(24.2)	15	(24.2)
11-13 years	18	(29.0)	25	(40.3)
More than 11 years	29	(46.8)	22	(35.5)
Employment				
Full-time paid	30	(51.6)	29	(46.8)
Part-time paid	19	(30.6)	20	(32.3)
Self-employed	3	(4.8)	1	(1.6) #
Not in paid employment	8	(12.9)	12	(19.4)

Size of expected frequencies assumption not met

Table 6
Health characteristics and menopausal status for HRT user and non-user groups showing number of participants and percentage in each group, and significant differences between groups (χ^2 tests).

	HRT users (n = 62)		Non-users (n = 62)	
Exercise				
Regular exercise	42	(67.7%)	50	(80.6%)
No regular exercise	20	(32.3%)	12	(19.4%)
Smoking				
Never smoked	32	(51.6%)	43	(69.4%)
Past smoker	24	(38.7%)	11	(17.7%)*
Current smoker	6	(9.7%)	8	(12.9%)
Family history of:				
Strokes or TIA's	18	(29.0%)	16	(25.8%)
Dementia	7	(11.3%)	10	(16.2%)
No family history of above	41	(66.1%)	41	(66.1%)
Participant history of:				
Diabetes	1	(1.6%)	-	- #
High blood pressure	7	(11.3%)	9	(14.5%)
Heart disease	-	-	2	(3.2%) #
Cancer	5	(8.1%)	3	(4.8%) #
Depression	14	(22.6%)	7	(11.3%)
Pre-menstrual tension	29	(46.8%)	23	(37.1%)
Menopausal status				
Perimenopausal	19	(30.6%)	35	(56.5%)**
Postmenopausal	43	(69.4%)	27	(43.5%)
History of gynaecological surgery				
Hysterectomy	28	(45.2%)	10	(16.1%)**
Ovaries removed	10	(16.2%)	3	(4.8%)*
Use of concomitant medications				
Yes	39	(62.9%)	29	(46.8%)
No	23	(37.1%)	33	(53.2%)

**$p<.01$ *$p<.05$ # Size of expected frequencies assumption not met

Table 5 shows the differences between the HRT group and non-HRT group for ethnicity, education and employment. Chi square analysis revealed no significant differences between the groups for those of NZ European or European ethnicity, education, full- and part-time paid employment and those not in paid employment.

Table 6 shows the differences between the groups on health characteristics and menopausal status. Chi square analysis revealed no significant differences between the groups in exercise; family history of neurological conditions; participant history of high blood pressure, depression and pre-menstrual tension; or use of concomitant medication. However, significant differences between the groups were found for smoking, $\chi^2(2) = 6.73, p<.05$; menopausal status, $\chi^2(2) = 8.40, p<.01$; hysterectomy, $\chi^2(1) = 9.49, p<.0.1$; and ovarian surgery, $\chi^2(1) = 4.21, p< .05$. Examination of the observed cell frequencies indicated that, in this sample, HRT users were more likely to be past smokers than non-users; that women who have experienced surgical menopause were more likely to be HRT users than women who experience natural menopause; that women who had ovaries removed were more likely to be HRT users than women who had intact ovaries; and that women in perimenopause were more likely not to be HRT users.

Independent t-tests were conducted to test for differences between the HRT users and non-users on the interval level variables. This analysis revealed no significant differences between the groups on measures of age, IQ, stress or self-rated health. Group comparison means and standard deviations for these variables are shown in Table 7.

Table 7
Means and standard deviations for age, IQ based on NART, self-rated health, and total stress score for HRT users and non-user groups.

	HRT users (n = 62)		Non-users (n = 62)	
	Mean	(SD)	Mean	(SD)
Age in years	51.58	(4.80)	51.16	(4.21)
IQ based on NART errors	113.26	(9.26)	110.26	(11.73)
Self-rated health	1.97	(0.97)	1.89	(0.96)
Total stress score	8.29	(4.03)	7.68	(3.95)

Table 8
Means and standard deviations for subscales and total raw scores of the RBMT-E between HRT users and non-users, and significant differences between groups (t-tests).

	HRT users (n = 62)		Non-users (n = 62)	
	Mean	(SD)	Mean	(SD)
First names	4.58	(1.42)	4.16	(1.44)
Second names	3.47	(1.91)	3.50	(1.65)
Belongings/Appointments	10.35	(2.08)	9.61	(2.66)
Picture recognition	15.08	(3.16)	14.20	(2.57)
Story (immediate)	9.32	(3.16)	8.02	(3.67)*
Story (delayed)	8.53	(3.21)	6.89	(3.60)**
Face recognition	13.31	(1.41)	12.95	(1.84)
Route (immediate)	12.84	(2.35)	12.77	(2.41)
Route (delayed)	12.81	(2.43)	12.74	(2.35)
Messages (immediate)	5.85	(0.44)	5.82	(0.59)
Messages (delayed)	5.53	(0.97)	5.61	(0.75)
Orientation and date	13.60	(0.61)	13.42	(0.74)
Total raw score	115.27	(10.30)	109.52	(12.54)**

**$p<.01$ *$p<.05$

Table 8 reports the means and standard deviations for the RBMT-E subscales and total raw scores and shows that there were significant differences between the groups on Story immediate, $t(122) = 2.12$, $p<.15$, Story delayed, $t(122) = 2.68$, $p=<.01$, and the Total raw score, $t(122) = 2.79$, $p<.01$. These results indicate that HRT users have better everyday memory than non-users, particularly verbal memory both immediate and delayed.

Table 9 reports the mean and standard deviations for the Digit Span measures of short-term attention and working memory. Independent t-tests showed there were no significant differences between the groups.

Table 9
Means and standard deviations for Digit Span for HRT users and non-users.

	HRT users (n = 62)		Non-users (n = 62)	
	Mean	(SD)	Mean	(SD)
Digit Span Forward	10.85	(2.48)	10.69	(2.41)
Digit Span Backward	6.52	(2.09)	6.89	(2.48)

Table 10
Means and standard deviations for the Positive and Negative Affect Schedule (PANAS) for HRT users and non-users.

	HRT users (n = 62)		Non-users (n = 62)	
	Mean	(SD)	Mean	(SD)
Positive affect	33.19	(6.88)	32.50	(8.13)
Negative affect	15.73	(6.56)	16.31	(6.90)

Table 10 reports the means and standard deviations for PANAS. Independent t-tests showed there were no significant differences between the groups on either positive or negative affect.

Table 11 reports the means and standard deviations for the POMS mood scale. Although the HRT group had slightly higher mean scores on the subscales of Depression, Anger, Fatigue and on the Total mood disturbance score indicating a more negative mood state, independent t-tests showed there were no significant differences between the groups on any of the subscales or on the Total mood disturbance score.

Table 11
Means and standard deviations for the subscales and Total mood disturbance score of POMS for HRT users and non-users.

	HRT users (n = 62)		Non-users (n = 62)	
	Mean	(SD)	Mean	(SD)
Anxiety	7.24	(5.93)	8.40	(6.57)
Depression	7.81	(9.87)	6.82	(7.47)
Anger	7.47	(7.90)	6.45	(6.13)
Fatigue	10.05	(6.86)	9.35	(6.23)
Confusion	6.47	(5.03)	7.37	(4.93)
Vigour	16.95	(6.81)	16.76	(6.75)
Friendliness	18.16	(4.02)	18.09	(4.70)
Total mood disturbance score	54.08	(33.97)	53.65	(27.64)

Table 12 reports the means and standard deviations for the two groups on the WHQ. Independent t-tests showed an expected significant difference between the two groups on the Vasomotor subscale, $t(122)= -4.14$, $p<.001$. Overall, the mean scores are lower for the HRT group reflecting a higher level of well-being.

Table 12
Means and standard deviations for the subscales and Total Wellbeing score of WHQ for HRT users and non-users, and significant differences between the groups (t-tests).

	HRT users (n = 62)		Non-users (n = 62)	
	Mean	(SD)	Mean	(SD)
Depression	.66	(.53)	.67	(.46)
Anxiety	.76	(.66)	.79	(.69)
Somatic problems	1.16	(.59)	1.17	(.59)
Memory problems	1.48	(.73)	1.65	(.69)
Vasomotor symptoms	.77	(.98)	1.56	(1.14)***
Sexual difficulties	.92	(.81)	.94	(.74)
Sleep disturbance	1.37	(.74)	1.45	(.79)
Menstrual problems	.74	(.58)	.98	(.74)
Attractiveness	1.40	(.61)	1.48	(.64)
Total well-being score	.96	(.42)	1.10	(.39)

***$p<.001$

Longitudinal sample

In this sample (n = 17), none of the demographic variables changed between pre-HRT (before HRT use) and post-HRT (after HRT use) interviews. Nor was there any change on: exercise (59% regular exercisers) smoking (no current smokers, 29.4% past smokers, 70.6% never smoked) family history of neurological conditions (17.6% strokes, 17.6% dementia, 64.7% no family history of neurological conditions, 5.9% history unknown) participant history of high blood pressure (5.9%) depression (11.8%) or pre-menstrual tension (41.2%). In this sample 17.6% had undergone hysterectomy, 17.6% had undergone ovarian surgery, 70.6% were perimenopausal and 29.4% were postmenopausal.

Binomial sign tests revealed no significant differences between the pre-HRT and post-HRT interviews in use of concomitant medications. Repeated measures t-tests revealed no significant differences between pre-HRT and post-HRT in stress or self-rated health.

Table 13 reports the means and standard deviations for the RBMT-E subscales and total raw score. Repeated measures t-tests showed there were significant differences from pre-HRT to post-HRT on: Story immediate, $t(16) = -4.55$, $p<.001$; Story delayed, $t(16) = -4.37$, $p<.001$; Route immediate, $t(16) = -3.40$, $p<.01$; Route delayed, $t(16) = -2.82$, $p<.05$; Orientation and date, $t(16) = -2.22$, $p<.05$; and Total raw score, $t(16) = -6.01$, $p<.001$. These results indicate that everyday memory is enhanced by HRT use.

Table 13
Means and standard deviations for subscales and total raw scores of the RBMT-E for pre-HRT and post-HRT interviews, and significant differences between the groups (t-tests).

	Pre-HRT (n = 17)		Post-HRT (n = 17)	
	Mean	(SD)	Mean	(SD)
First names	3.94	(1.43)	4.47	(1.50)
Second names	2.94	(1.82)	2.88	(1.62)
Belongings/Appointments	9.71	(2.66)	10.47	(2.37)
Picture recognition	13.29	(3.98)	14.88	(1.87)
Story (immediate)	7.88	(2.76)	10.94	(3.34)***
Story (delayed)	6.82	(2.67)	10.53	(3.52)***
Face recognition	13.35	(1.06)	13.18	(1.42)
Route (immediate)	12.06	(2.36)	14.00	(1.77)**
Route (delayed)	12.29	(2.64)	14.00	(1.77)*
Messages (immediate)	5.65	(0.70)	6.00	(0.00)
Messages (delayed)	5.76	(0.56)	5.76	(0.66)
Orientation and date	13.18	(0.73)	13.65	(0.61)*
Total raw score	106.71	(6.68)	120.76	(11.21)***

***$p<.001$ **$p<.01$ *$p<.05$

Table 14 reports the means and standard deviations for Digit Span Forward and Digit Span Backward. Repeated measure t-tests showed there was a significant difference in short-term working memory from pre-HRT to post-HRT, $t(16) = -2.67$, $p<.05$. This result indicates that working memory is enhanced by HRT use.

Table 14
Means and standard deviations for Digit Span Forward and Digit Span Backward for pre-HRT and post-HRT interviews, and significant differences between the groups (t-tests).

	Pre-HRT (n = 17)		Post-HRT (n = 17)	
	Mean	(SD)	Mean	(SD)
Digit Span Forward	10.53	(2.37)	10.12	(2.00)
Digit Span Backward	5.76	(2.39)	6.65	(2.55)*

* $p<.05$

Table 15 reports the means and standard deviations for PANAS. Repeated measure t-tests showed a significant difference in Positive Affect, $t(16) = -3.03$, $p<.01$, and Negative Affect, $t(16) = 2.44$, $p<.05$ between pre-HRT and post-HRT interviews.

Table 15
Means and standard deviations for PANAS for pre-HRT and post-HRT interviews, and significant differences between the groups (t-tests).

	Pre-HRT (n = 17)		Post-HRT n = 17	
	Mean	(SD)	Mean	(SD)
Positive affect	31.59	(6.21)	35.35	(5.89)**
Negative affect	16.83	(7.29)	12.72	(2.14)*

**$p<.01$ *$p<.05$

Table 16 reports the means and standard deviations for the POMS subscales and Total mood disturbance score and shows that there was a significant difference in mood between pre-HRT and post-HRT interviews on: Anxiety, $t(16) = 2.49, p<.05$; Fatigue, $t(16) = 3.13, p<.01$; Confusion, $t(16) = 4.14, p<.01$; Vigour, $t(16) = -4.30, p<.01$; Total mood disturbance score, $t(16) = 4.14, p<.01$. These results indicate that negative aspects of mood are reduced and positive aspects are enhanced by HRT use.

Table 16
Means and standard deviations for the subscales and total mood disturbance score of POMS for pre-HRT and post-HRT interviews, and significant differences between the groups (t-tests).

	Pre-HRT (n = 17)		Post-HRT (n = 17)	
	Mean	(SD)	Mean	(SD)
Anxiety	8.00	(5.45)	4.82	(3.13)*
Depression	5.18	(3.91)	2.94	(2.95)
Anger	5.35	(4.95)	4.29	(3.53)
Fatigue	10.59	(6.76)	6.00	(5.05)*
Confusion	8.59	(4.69)	4.76	(3.56)*
Vigor	15.12	(5.31)	19.24	(4.34)**
Friendliness	16.82	(5.02)	16.35	(3.79)
Total mood disturbance score	54.59	(20.81)	35.59	(14.01)**

**$p<.01$ *$p<.05$

Table 17 shows the means and standard deviations for the WHQ. Repeated measure t-tests showed that there was a significant difference in well-being between pre-HRT and post-HRT interviews on: Depression, $t(16) = 3.41, p<.01$; Anxiety, $t(16) = 2.53, p<.05$; Somatic problems, $t(16) = 2.12, p<.05$; Memory problems, $t(16) = 13.14, p<.001$; Vasomotor symptoms, $t(16) = 7.83, p<.001$; Sexual problems, $t(16) = 2.63, p<.05$; Sleep disturbance, $t(16) = 2.60, p<.05$; Attractiveness, $t(16) = 2.16, p<.05$; and the Total Well-

being score, $t(16) = 7.26, p<.001$. These results indicate that the overall well-being of women improves with HRT use.

Table 17
Means and standard deviations for the subscales and Total Wellbeing score of the Women's Health Questionnaire (WHQ) for pre-HRT and post-HRT interviews, and significant differences between the groups (t-tests).

	Pre-HRT (n = 17)		Post-HRT (n = 17)	
	Mean	(SD)	Mean	(SD)
Depression	.63	(0.54)	.38	(0.39)**
Anxiety	.60	(0.57)	.29	(0.25)*
Somatic problems	1.00	(0.55)	.76	(0.39)*
Memory problems	1.80	(0.67)	.60	(0.19)***
Vasomotor symptoms	2.26	(0.92)	.29	(0.44)***
Sexual difficulties	1.20	(0.79)	.90	(0.81)**
Sleep disturbance	1.43	(0.68)	1.00	(0.65)*
Menstrual problems	.88	(0.51)	.81	(0.63)
Attractiveness	1.59	(0.62)	1.29	(0.69)*
Total well-being score	1.27	(0.38)	.70	(0.28)***

***$p<.001$ **$p<.01$ *$p<.05$

8.3 *Hypothesis testing*

8.3.1 Hypothesis 1

HRT use will be associated with increased positive affect, decreased negative affect, and improvement in mood states, while accounting for the effects of stressful life events, self-rated health, sleep problems, vasomotor symptoms, and exercise among perimenopausal and postmenopausal women.

Cross-sectional sample

The bivariate correlations shown in Table 18, indicate that there were no significant relationships between HRT use and Positive Affect, Negative Affect, or the Total mood disturbance scores. Neither were there any significant correlations between the individual mood states and HRT use. Independent t-tests confirmed that there was no difference between HRT users and non-users on measures of Positive Affect, Negative Affect, the individual mood states, or Total mood disturbance scores. This hypothesis was therefore not supported.

However, the correlations do indicate that both a higher level of negative affect and a higher mood disturbance score are associated with higher levels of stressful life events, sleep problems, and not taking regular exercise. A higher mood disturbance score is also associated with a poorer perception of health. Also, a lower level of positive affect is associated with sleep problems. The correlations confirm that a reduction in vasomotor symptoms is related to HRT use and indicate that the presence of these symptoms is related to a decrease in positive affect and an increase in sleep disturbance. There was also a weak but significant correlation ($r=.153$ $p<.05$) between the mood state of confusion and vasomotor symptoms.

Table 18
Pearson's r correlation coefficients for HRT status, Positive Affect, Negative Affect, Total Mood Disturbance, stressful life events, health status, sleep problems, exercise, and vasomotor symptoms (n = 124).

	HRT status	Positive affect	Negative affect	Total Mood Disturbance	Stressful life events	Health status	Sleep problems	Exercise
HRT status								
Positive affect	.05							
Negative affect	-.04	-.15*						
Total Mood Disturbance	.01	-.45**	.79**					
Stressful life events	.08	-.07	.24**	.30**				
Health status	.04	-.07	.13	.23**	.32**			
Sleep problems	-.05	-.24**	.24**	.34**	.18*	.27**		
Exercise	.15	-.03	.15*	.28**	.19*	.29**	.15*	
Vasomotor symptoms	-.35**	-.16*	.01	.05	.01	.14	.29**	.010

*$p<.05$ **$p<.01$

Additional analysis was undertaken to investigate whether there were any differences on the mood variables between HRT users and non-users within menopausal status or type of menopause. There were no significant correlations between menopausal status or type of menopause and HRT use, positive affect, negative affect, the total mood disturbance score, or any of the POMS subscales. Also, independent t-tests showed that, among HRT users, there were no significant differences on any of the mood variables between women who took oestrogen only and those who took oestrogen plus progesterone.

Longitudinal sample

The repeated measure t-tests showed significant differences between pre-HRT and post-HRT scores on Positive Affect, Negative Affect (see Table 15), the Total mood disturbance score, and the subscales of Anxiety, Fatigue, Confusion, and Vigour (see Table 16). The post HRT scores for Positive Affect and the subscale of Vigour were significantly higher than pre-HRT scores indicating a higher level of these mood states. The post HRT scores for Negative Affect, the Total mood disturbance score, and the subscales of Anxiety, Fatigue and Confusion were significantly lower than pre-HRT scores indicating lower levels of these negative mood states. This result supported the hypothesis that HRT use would improve mood.

In order to test whether HRT use explained the improvement in mood or whether the change could be accounted for by exercise or change in stressful life events, self-rated health, sleep problems, and vasomotor symptoms, the bivariate correlations of the change scores on the mood variables which showed significant difference and the potential confounding variables of change in stressful life events, self-rated health,

vasomotor symptoms, sleep problems, and exercise were examined. These correlations, reported in Table 19, show that changes in stressful life events, self-rated health, vasomotor symptoms and sleep were not associated with change on the mood variables. However, there were significant relationships between exercise and Positive Affect and Vigour.

Table 19
Pearson's r correlation coefficients for mood change scores and the change variables of stressful life events, self-rated health, vasomotor symptoms, sleep problems, and exercise (n = 17).

	Positive Affect change	Negative Affect change	Total mood Disturbance change	Anxiety change	Fatigue change	Confusion change	Vigour change
Stressful life events change	.26	.26	.30	-.16	-.30	.28	.25
Self-rated health change	.39	-.08	-.19	.25	.39	.31	.28
Vasomotor symptom change	.44	.37	.46	-.38	-.21	-.16	.32
Sleep change	-.12	.19	.07	-.33	.11	.26	-.29
Exercise	-.50*	-.13	.14	.08	-.02	-.20	-.51*

* $p = <.05$

To test the first hypothesis while accounting the the effect of exercise two-way mixed design ANOVAs were conducted with Positive Affect and Vigour as the dependent variables. In both analyses the assumptions of normality and homogeneity of variance were met. The assumption of homogeneity of intercorrelations was met as Box's M was not significant ($p > .001$).

In the first analysis, the within-subject factor was HRT with two levels (pre-HRT and post-HRT), the between-subject factor was exercise with two levels (regular exercise

and no regular exercise), and the dependent variable was the Positive Affect score. The main effect for HRT was significant, $F(1,15) = 13.86, p = .002$. The strength of the relationship between the HRT factor and the dependent variable was strong, as assessed by partial η^2 (.48), with the HRT factor accounting for 48% of the variance of the difference in Positive Affect scores between pre-HRT and post-HRT while accounting for differences in exercise. The interaction between HRT and exercise was significant, $F(1,15) = 4.92, p = .04$.

Table 20
Estimated marginal means of pre-HRT and post-HRT Positive Affect scores for regular exercisers and non-exercisers (n = 17)

Exercise	HRT	Mean	Std. Dev.	N
Regular exercise	pre-HRT	33.20	1.92	10
	post-HRT	34.90	1.92	10
No regular exercise	pre-HRT	29.29	2.30	7
	post-HRT	36.00	2.29	7

Table 20 reports the estimated marginal means and shows that the improvement in Positive Affect is different for the two groups. Less improvement on the Positive Affect score was shown by regular exercisers (34.90 - 33.20 = 1.70) than by non-regular exercisers (36.00 - 29.29 = 6.71).

In the second two-way mixed design ANOVA, the within-subject factor was HRT, the between-subject factor was exercise, and the dependent variable was the Vigour score. The main effect for HRT was significant, $F(1,15) = 23.04, p = .001$. The strength of the relationship between the HRT factor and the dependent variable was strong, as assessed by partial η^2 (.61), with the HRT factor accounting for 61% of the variance of the

difference in Vigour scores between pre-HRT and post-HRT while accounting for differences in exercise. The interaction between HRT and exercise was not significant.

8.3.2 Hypothesis 2

HRT use will be associated with improved short-term attention, short-term working memory, everyday memory, and verbal memory while accounting for the effects of age, IQ, education and memory-affecting medications, among peri-menopausal and post-menopausal women.

The checking of concomitant medications for any effect they may have on memory revealed that no participants were taking any medications that fell into this category. Therefore this possible confounding variable was not used in the following analyses.

Cross-sectional sample

The correlation coefficients reported in Table 20 indicate that HRT use is not significantly related to short-term attention as measured by Digit Span Forward or to short-term working memory as measured by Digit Span Backward. Independent t-tests (see Table 9) confirmed that there was no difference between HRT users and non-users on these measures.

Table 21 does indicate that everyday memory, as measured by the RBMT-E total score, and verbal memory as measured by the Story Immediate and Story Delayed sub-scales of the RBMT-E were significantly related to HRT status, IQ and education, and that the RBMT-E score was related to age. Independent t-tests (see Table 8) confirmed differences between HRT users and non-users on these memory variables and therefore

three hierarchical multiple regression analyses were conducted to evaluate the impact of HRT use on everyday memory and verbal memory while controlling for the effects of age, IQ, and education.

Table 21
Pearson's r correlation coefficients for RBMT-E total raw score, Digit Span Forward, Digit Span Backward, Story Immediate, Story Delayed and HRT status, age, IQ, and education (n = 124).

	RBMT-E	Digit Span Forward	Digit Span Backward	Story Immediate	Story Delayed
HRT status	.25**	.03	-.08	.19*	.24**
Age	-.20*	-.06	.05	-.07	-.09
IQ	.47**	.39**	.37**	.43**	.39**
Education < 11 years	-.34**	-.28*	-.31**	-.39**	-.33**
Education 11-13 years	-.04	.08	.03	-.01	-.03
Education > 13 years	.34**	.12	.24**	.35**	.32**

*p<.05 **p<.01

Level of education was measured as a discrete variable with participants falling into three categories. For regression analysis this was converted into dichotomous variables by dummy variable coding. Two dichotomous variables were entered into the analysis. 'Education 1' compared those with less than 11 years of education with those with 11 years and more. 'Education 2' compared those with more than 13 years of education with those with 13 years and less.

In all three analyses, the assumptions for hierarchical multiple regression were met. With 124 participants and 4 independent variables, the cases-to-IV ratio was 31:1, thus meeting the requirements for analysis (Tabachnik & Fidell, 1989). There were no

extreme outliers. Analysis of the residuals indicated that the assumptions of normality, linearity, and homoscedasticity were met and therefore no transformation of the variables was necessary.

In the first regression analysis, the RBMT-E total raw score was entered as the dependent variable. Table 22 shows that, at step one, the effect of the combination of age, IQ, and education on the total RBMT-E score was significant (adjusted $R^2 = .24$, $F(4,119) = 10.47$, $p<.01$). This indicates that these variables account for 24% of the variance in the everyday memory score. However, the relative impact of these variables differed as shown by the standardised coefficients (β) in Table 22. Only age and IQ had a significant impact indicating that, while younger women with a higher IQ tended to have higher everyday memory scores, level of education had no impact when age and IQ were accounted for.

Table 22
Hierarchical regression analysis of the effects of age, IQ, education, and HRT status on total RBMT-E score (n = 124)

	Step 1 β	Step 2 β
Age	-.16*	-.17*
IQ	.37**	.33**
Education 1	-.10	.12
Education 2	.08	.06
HRT status		.20*
R^2	.26 **	.30*
Adjusted R^2	.24**	.27*
R^2 change		.04*

*$p<.05$ **$p<.01$

At step two, the effect of the combination of age, IQ, education and HRT status on the total RBMT-E score was significant (adjusted $R^2 = .27$, $F(1,118) = 6.4$, $p<.05$) indicating that these variables account for 27% of the variance in the everyday memory score. It also indicated that HRT status had an effect over and above that of age, IQ, and education (R^2 change = .04). These results suggest that women who have similar IQ levels and are the same age are likely to have higher everyday memory scores if they are HRT users.

In the second regression analysis, the Story Immediate score was entered as the dependent variable. Table 23 shows that, at step one, the effect of the combination of age, IQ, and education on the Story Immediate score was significant (adjusted $R^2 = .21$, $F(4,119) = 9.02$, $p<.01$). This indicated that these variables account for 21% of the variance in the immediate verbal memory score. However, the relative impact of these variables differed. Only IQ and education had a significant impact indicating that, while women with a higher IQ tended to have a higher immediate verbal score, those with less than 11 years of education tended to have lower scores.

At step two, the effect of the combination of age, IQ, education and HRT status on the Story Immediate score was significant (adjusted $R^2 = .22$, $F(4,119) = 3.22$. $p<.05$) indicating that these variables account for 22% of the variance in the immediate verbal memory score. However, while the impact of IQ and the lower level of education retained a significant impact, HRT status had no significant effect over and above these variables. These results suggest that while IQ and a lower level of education do make a difference to immediate verbal memory, HRT use does not.

Table 23
Hierarchical regression analysis of the effects of age, IQ, education, and HRT status on the Story Immediate score (n = 124)

	Step 1 β	Step 2 β
Age	-.02	-.03
IQ	.26*	.24*
Education 1	-.21*	-.22*
Education 2	.11	.10
HRT status		.15
R^2	.23 **	.25*
Adjusted R^2	.21**	.22*
R^2 change		.02

*p<.05 **p<.01

In the third regression analysis, the Story Delayed score was entered as the dependent variable. Table 24 shows that, at step one, the effect of the combination of age, IQ, and education on the Story Delayed score was significant (adjusted R^2 = .21, F (4,119) = 6.85, p<.01. This indicates that these variables account for 16% of the variance in the delayed verbal memory score. However only IQ had a significant impact indicating that women with a higher IQ tended to have a higher delayed verbal memory score.

At step two, the effect of the combination of age, IQ, education and HRT status on the Story Delayed score was significant (adjusted R^2 = .19, F (1,118) = 5.7, p<.05) indicating that these variables account for 19% of the variance in the delayed verbal memory score. It also indicated that HRT status had an effect over and above that of age, IQ, and education (R^2 change = .04). These results suggest that women who have similar IQ levels are likely to have higher delayed verbal memory scores if they are HRT users.

Table 24
Hierarchical regression analysis of the effects of age, IQ, education, and HRT status on the Story Delayed score (n = 124)

	Step 1 β	Step 2 β
Age	-.05	-.06
IQ	.26*	.23*
Education 1	-.15	-.17
Education 2	.11	.09
HRT status		.20*
R^2	.19**	.22*
Adjusted R^2	.16**	.19*
R^2 change		.04*

*p<.05 **p<.01

Longitudinal sample

The repeated measure t-tests showed significant differences between pre-HRT and post-HRT scores on short-term working memory as measured by Digit Span Backward, everyday memory as measured by the total raw score of the RBMT-E, and verbal memory as measured by Story Immediate and Story Delayed sub-scales of the RBMT-E (see Tables 13 & 14). By the nature of the study design, the participants for this sample acted as their own controls for age, IQ and education and therefore the results from this sample support the hypothesis for the above-mentioned memory variables.

Additional analysis was carried out to investigate whether there was any relationship between the change variables of short-term memory, everyday memory and verbal memory, and age, IQ and education in order to determine whether these factors could account for the improvement in memory (eg if participants with higher IQ improved their score more than participants with lower IQ). There were no significant

correlations between the change variables of memory and age and IQ. One-way analyses of variance (ANOVA) showed no significant relationships between the change variables of memory and level of education.

8.3.3 Hypothesis 3

The relationship between memory and HRT use will be mediated by mood.

In order to test the model in which the effect of HRT use on memory is mediated by mood, a set of conditions must be met (Baron & Kenny, 1986): (a) the independent variable, HRT use, must be significantly related to the mediator, mood; (b) the mediator, mood, must be significantly related to the dependent variable, memory; (c) the independent variable, HRT use, must be significantly related to the dependent variable,memory; (d) when both of the relationships in (a) and (b) above are controlled, the previously significant relationship in (c) is no longer significant, or is at least significantly reduced.

Cross-sectional sample

As it has been established that there is no relationship between mood and HRT use, condition (a) is not met and therefore this hypothesis is not supported.

Longitudinal sample

It has been established that there is a relationship between HRT use and Positive Affect, Negative Affect, Total mood disturbance, and the subscales of Anxiety, Fatigue, Confusion, and Vigour. There is also a relationship between HRT use and everyday memory, short-term attention, short-term working memory, and delayed verbal

memory. Thus, conditions (a) and (c) are met. In order to examine condition (b), that there is a significant relationship between mood and memory, correlations between the change scores of the memory and mood variables were examined. There were no significant relationships between any of the mood change variables and the memory change variables. Therefore condition (b) was not met and it can be concluded that Positive Affect, Negative Affect, Total mood disturbance, and the subscales of Anxiety, Fatigue, Confusion, and Vigour do not mediate the relationship between HRT use and everyday memory, short-term working memory, and immediate and delayed verbal memory.

CHAPTER 9

DISCUSSION

9.1 *Summary of results*

This study was designed to examine the effects of HRT on mood and memory in mid-life women. Two mutually exclusive samples were used, a cross-sectional sample which was used to compare the differences on mood and memory between HRT-users and non-users, and a longitudinal sample which was used to examine the change over time from before HRT use to three months after HRT use. The samples comprised women who were, on average, both physically and psychologically healthy. The results from both samples indicate that HRT use is associated with improvement in everyday memory and that this improvement is not secondary to mood change. However, there were differences in results between the samples and these will be discussed for each hypothesis.

9.1.1 *Hypothesis 1*

The hypothesis that HRT use would be associated with improved mood was supported in the longitudinal sample but not in the cross-sectional sample. In the cross-sectional sample there was no difference between HRT users and non-users on any of the mood states, regardless of menopausal status or type of menopause, indicating that HRT use is not associated with improved mood. Neither was there any difference in mood, among HRT users, between women who used oestrogen only and those who used a combination of oestrogen and progesterone. In the longitudinal sample, taking HRT for three months was associated with an increase in feelings of positive affect and of vigour

and a decrease in feelings of negative affect, anxiety, fatigue and confusion, and in overall mood disturbance. These effects were maintained when differences in exercise habits were accounted for and when changes in stressful life events, self-rated health, sleep problems, and vasomotor symptoms were taken into account. This result indicates that, in the short-term, HRT is associated with improved mood.

To explain the different results from the two samples, the descriptive statistics of the two samples were examined and compared to see if there were any substantial differences between them. A major difference was the recruitment source of the participants. The cross-sectional sample was predominantly recruited through the press release (75%) and is therefore mainly a community sample, whereas the longitudinal sample was recruited mainly through medical practitioners (86.7%) and is therefore mainly a clinical sample. If the different samples are looked at in this way, the results of both add support to previous research.

Although the majority of previous research which has looked at the effect of HRT on mood has been in the form of prospective clinical trials, two cross-sectional studies (France, Lee, & Schofield,1996; Slaven & Lee, 1998) have used community samples to compare differences in mood and well-being between HRT users and non-users. In both these studies no differences were found in mood between HRT users and non-users; results which are reflected in the present study. The result for the longitudinal sample in this study lends support to two studies (Derman, Dawood & Stone, 1995; Sherwin, 1988) which found that, in prospective clinical trials on clinical samples, over a period of 2-4 months, women who received oestrogen had improved mood compared

to those who had not.

However, if the longitudinal sample was a clinical sample it could be expected to differ from the cross-sectional sample on rates of gynaecological surgery and negative mood scores as it has been established that those who seek clinical help for menopausal symptoms differ on these variables (Morse et al, 1994). This was not the case. A similar percentage of women in both the samples had undergone gynaecological surgery and the mean scores on all the measurements of mood were similar for the cross-sectional sample and the longitudinal sample at the pre-HRT interview. Thus, the difference in source of recruitment between the samples does not indicate that they are from different populations of mid-life women.

Another difference between the two samples was that a much higher percentage of women in the longitudinal sample were perimenopausal (71%) compared with the cross-sectional sample (44%). Although research (e.g. Hunter, 1990; Lee & Taylor, 1996) has shown that mild depressive symptoms peak in perimenopause, the similarity of mood scores of the two samples makes it unlikely that this difference in menopausal status between the groups accounts for the different results. It has been suggested by Avis and McKinlay (1990) in their investigation of health-care utilization of mid-life women, that perimenopausal women differ most from women of other menopausal statuses in that they talked to medical practitioners about menstrual change or problems. It is most likely therefore that the longitudinal sample is not a clinical sample per se but rather one made up of women for whom menopausal symptoms were interfering with their lives and they sought answers from their medical practitioners for these problems.

In light of the failure of the differences between the two samples to explain the different result for this hypothesis, it is probable that the answer lies in problems associated with the design of the longitudinal aspect of the study. Although placebo control was not possible in this study, the placebo effect of HRT is important and cannot be ignored (Barlow, 1991). In the longitudinal sample, it is likely that the participants wanted and expected HRT to have beneficial effects. It is possible therefore these positive expectations may have influenced the subsequent rating of participants' mood. This effect could account for the substantial improvement in mood scores; an improvement which took the scores well above the established norms (McNair, Lorr & Droppleman, 1981).

Furthermore, although this study only aimed to look at the short-term effects of HRT, it is possible that a follow-up period of three months was not the optimum interval for accurate assessment of the effect of HRT on mood as the improvement in mood may be temporary and short-lived. It has mainly been controlled clinical trials which have shown a beneficial effect of HRT and these trials have only investigated short-term effects. An exception to these short-term trials was that of Campbell and Whitehead (1977) which used a double-blind, placebo-controlled, crossover trial and found that oestrogen treatment significantly improved mood at 4 months but found no improvement over placebo after 12 months. It is also of note that studies specifically designed to investigate the effect of oestrogen on serotonergic activity (Halbreich, 1997; Lippert, Filshie, Mück, Seeger & Zwirner, 1996) have also only examined short-term effects (60 days and 28 days respectively). It is therefore possible, and would to some extent explain the cross-sectional sample results, that the "mental tonic effect" (Utian,

1987) of exogenous oestrogen does not last; a factor that needs further investigation in light of the results that demonstrate that changes in vasomotor symptoms and sleep problems do not explain the substantial improvement in the mood of the longitudinal sample at the post-HRT interview.

As already mentioned, the mean scores on all the measurements of mood were similar for the cross-sectional sample and the longitudinal sample at the pre-HRT interview and both were lower on the negative aspects of mood than the established college student norms (McNair, Lorr & Droppleman, 1981), indicating that both samples had good psychological health. This finding is in agreement with a World Health Organisation report (1981) which concluded that no relationship has been established between the hormonal changes of menopause and psychological symptoms. However, it disagrees with the reviews of Pearce et al (1995) and Pearlstein et al (1997) which found that women who seek treatment for somatic or psychological symptoms at menopause have elevated depressive symptoms. The finding that there was no relationship between mood and either menopausal status (perimenopausal or postmenopausal) or type of menopause (natural or surgical), combined with the low scores on negative mood states, also disagrees with research which suggests that perimenopausal women and women who have undergone surgical menopause have elevated depressive symptoms (Ballinger, 1977; McKinlay et al, 1987). However, the samples in the present study were not randomly selected, they were volunteers who were fully informed about the nature of the research and what would be involved in participation and it is unlikely that women who were experiencing any depressive symptoms would have had the inclination to take part in the study. The samples cannot therefore be seen as

representative of the total population of mid-life women. Rather they represent psychologically healthy groups and the results should be interpreted within this context.

Also of interest was the finding that, among HRT users in the cross-sectional sample, there was no difference in mood between women who took oestrogen only and those who took oestrogen plus progesterone. Although women with a uterus are routinely prescribed oestrogen in combination with progesterone to avoid endometrial cancer, negative mood effects are produced by most progestogens due to their effect on neurotransmitters via central nervous system progesterone receptors (Panay & Studd, 1997). Previous research has supported this effect of progesterone on mood. Dennerstein et al (1979) found that when a progestogen was added to oestrogen, the beneficial effects on mood were reduced, a conclusion which was supported by Holst, Backstrom, Hammarback and van Schoultz (1989) and Paterson (1982). However, it is also suggested by Panay and Studd (1997) that different types of progestogens have different effects with some causing only mild adverse somatic effects. Because the present study did not investigate the type of progestogen used, any relationship which might exist between progesterone and negative mood may not have emerged.

The psychosocial theory of mood and menopause (McKinlay et al, 1987), which suggests that stressful life changes are more responsible for lower mood levels at menopause than biological changes, was supported by the cross-sectional sample but not by the longitudinal sample. The cross-sectional sample indicated that, although the supplementation of oestrogen did not influence mood, the experience of more stressful life events increased feelings of negative affect and total mood disturbance. Also, a

lower estimation of self-rated health was indicative of increased mood disturbance. The longitudinal sample indicated that the improvement in mood after taking HRT for three months was not related to any change in stressful life events or health status, rather that it was predominantly related to the oestrogen supplement. This sample therefore would appear to support the neurobiological theory (Halbreich, 1997) which suggests that oestrogen increases levels of the neurotransmitters which are associated with the regulation of mood: higher levels of the neurotransmitters being associated with higher levels of affect. However, the results from the longitudinal sample should be treated with caution because of the way in which the stress variable was measured and the question of what the stress change variable was actually measuring.

The measure used was an adaptation of Norbeck's (1984) Life Event Questionnaire which asked participants to think about stressful events which had happened in different areas of their lives over the past year and rate the level of stress experienced on a four-point scale. In light of the three month interval between interviews for the longitudinal sample, it would have been more expedient to have placed this time interval on the measure rather than a one year period so that a more accurate assessment of change could have been calculated. Also, to test this hypothesis, change scores were used to assess the relationship between stress and mood. Because of the acknowledged relationship between perception of stress and mood (Clark, Beck & Brown, 1992) and therefore the likelihood that the improvement in mood may have led the participants to make a more positive appraisal of their stressful life events, the stress change score was confounded by mood change and may not be an accurate assessment of stress change.

The results from the longitudinal sample support the neurobiological theory that mood symptoms are secondary to changes in reproductive hormones through the effect of oestrogen on neurotransmitter levels (Halbreich, 1997). However, the interaction of exercise in the HRT/mood relationship was an interesting, although not surprising finding. That women who exercise regularly had, on average, higher levels of positive affect before taking HRT than women who did not take regular exercise is consistent with the notion of the positive effects of exercise on mental health (Bouchard, Shephard, Stephens, Sutton & McPherson, 1990). That women who did not exercise regularly showed a significant improvement in positive affect after three months of HRT whereas those who take regular exercise did not show any substantial difference lends weight to the suggestion of Slaven and Lee (1994) that exercise may offer a healthy alternative to medication in alleviating some of the frequently reported psychological symptoms of menopause.

The domino theory (Dennerstein & Van Hall, 1986), which suggests that mood changes during menopause occur because of the negative impact of vasomotor symptoms, was not supported by either sample. However, in the cross-sectional sample it was found that vasomotor symptoms did impact on positive affect. Women who experienced more severe vasomotor symptoms had lower levels of positive affect, which could translate into lower energy and concentration levels. In the longitudinal sample, the reduction in vasomotor symptoms resulting from taking HRT was not related to mood change at all.

9.1.2 *Hypothesis 2*

The hypothesis that HRT use would be associated with improved memory received considerable support in both samples. In the cross-sectional sample, HRT use was associated with better everyday memory and immediate and delayed verbal memory and this effect was maintained for everyday memory and delayed verbal memory when age, IQ and level of education were accounted for. However, the differences in immediate verbal memory were found to be associated with IQ and level of education rather than HRT use: higher IQ being associated with higher immediate verbal memory scores and less than 11 years of education being associated with lower scores. In this sample, HRT use was not associated with either short-term attention or short-term working memory. In the longitudinal sample, HRT use was associated with improved everyday memory, short-term working memory, and both immediate and delayed verbal memory. HRT use was not associated with short-term attention.

These results generally support the hypothesis that HRT use will improve memory and lend general support to previous research that has shown the benefits of oestrogen use on cognitive function in women. While the result that women who take HRT have better delayed verbal memory than non-users supports the findings of Kampen and Sherwin (1994) in a cross-sectional study, and Sherwin and Tulandi (1996) in a longitudinal study, it does not support the findings of Sherwin (1988) and Phillips and Sherwin (1992). Although all these studies used similar tests (paragraph recall) and delay periods to the present research, the ones which found no effect of oestrogen on delayed verbal memory tested women before and after surgical menopause, a factor which may confound the effect of oestrogen on this aspect of memory.

The finding from the longitudinal sample that HRT use improved immediate verbal memory supports the findings of Sherwin (1988) and Sherwin and Tulandi (1996) who found that oestrogen served to maintain immediate verbal memory in women who had undergone hysterectomy and bilateral oophorectomy for benign disease. It also supports the study of Phillips and Sherwin (1992) who found that oestrogen improved the scores on immediate paragraph recall postoperatively compared to baseline in women who underwent the same surgery. All three of these studies were repeated-measures design and used paragraph recall as a test of verbal memory. In the cross-sectional sample of the present study, the significant difference between HRT-users and non-users on scores of immediate verbal memory was found to be due to differences in IQ and education levels. A comparable study by Kampen and Sherwin (1994), in which there were no differences between oestrogen users and non-users in years of education did find a significant difference between users and non-users on immediate verbal memory. However, this study did not control for IQ level, a factor which is of importance for a generation of women who may not have been encouraged into higher education despite their innate ability. Other studies, which matched their samples on IQ (Jacobs et al, 1998; Kimura, 1995; Resnick et al, 1998) and found a positive effect of HRT on verbal memory, used tests which involved remembering unrelated words and may not therefore be comparable to the results of this study.

These findings for verbal memory are therefore only partially consistent with previous research and the neuroscientific evidence of the effects of oestrogen on memory. They, together with the finding that short-term attention is not affected by exogenous oestrogen, are inconsistent with the suggestion of Phillips and Sherwin (1992) that

oestrogen may enhance attention abilities in the short-term but not long-term.

The effect of oestrogen on working memory, which was found to improve in HRT users in the longitudinal sample, has only been investigated in one other study (Schmidt et al, 1996) and no effect was found. Although working memory is not specifically measured in the RBMT-E, it can be seen as an integral part of the test (Glass, 1999), and the improvement found in overall everyday memory can be seen as supportive of this result. As working memory is involved in the manipulation of material, the findings from this study support the suggestion that concentration is enhanced by oestrogen (Phillips & Sherwin, 1992).

While there are no published studies which have examined the effects of HRT on everyday memory in a comprehensive way with which to compare this study, these results indicate that, overall, the complaints which mid-life women have about their memories in their day-to-day lives, are improved with HRT use. This study therefore lends support to the suggestion by Warga (1999) that it is the problems of memory, as experienced by women themselves, which should be examined when investigating the effect of HRT on cognition. However, while the RBMT-E undoubtedly tested many of the memory complaints which mid-life women experience, a factor frequently commented on by participants, it was of note that no significant differences were found in either sample for remembering names, recognising faces, remembering appointments or location of belongings. The only sub-tests which showed significant differences in both samples were those of immediate and delayed verbal memory. In addition, in the longitudinal sample, significant differences were found for the immediate and delayed

route around a room and for questions of orientation.

A probable explanation for the lack of difference in many of the sub-tests is that oestrogen has a selective effect on memory functions. Although the RBMT-E is designed as an overall test of everyday memory, its internal reliability coefficient was low (.63), an indication that the individual sub-tests measure different aspects of memory. Thus for example, while differences were found for paragraph recall which measures verbal memory, none were found for face recognition which measures visual recall. This may indicate that the different parts of the brain which are responsible for the different aspects of memory could also be differentially influenced by oestrogen.

However, the finding of improvement over time in the sub-tests of immediate and delayed route around a room and for questions of orientation is less likely to be due to the selective effect of oestrogen. It is more likely to be related to the effect of second testing. Although the parallel versions of the RBMT-E are designed to allow assessment both before and after an intervention (Wilson et al, 1999), it was suspected, and confirmed by some participants, that these sub-tests were completed more successfully at the second testing because the participants remembered their first testing experience. In the case of the route sub-test, although a different route was specified in each version, the testing was always done in the same room of the participants' homes and the questions related to orientation were identical for both versions and therefore a learning effect was almost inevitable. The improvement over time shown in these two sub-tests therefore needs to treated with caution. Furthermore, these results also indicate the need for a control/placebo group for the longitudinal sample. A matched

group of women not on HRT, or on a placebo, would have allowed assessment of the effect of second testing and given more strength to the finding that the improvement in everyday memory was related to HRT use.

Bearing in mind the likelihood of different aspects of memory being differentially influenced by oestrogen, the low reliability of the RBMT-E, and the obvious effects of second testing, the suitability of the RBMT-E as an accurate assessment of overall everyday memory for a non-clinical population may be brought into question. It may be more expedient to use selected sub-tests as measures of specific facets of memory in their own right rather than exacting a total score of uncertain meaning; an issue for investigation in future research in light of the results from the present study.

A factor of interest in this study was the low impact of age on memory. Although older women had slightly lower scores on the everyday memory tests, age was not related to any of the other aspects of memory tested. Although this low impact may be related to the restricted range of the sample (Tabachnick & Fidell, 1989), it is also likely to be related to the fact that most of the memory tests were concerned with short-term memory which shows virtually no change with age (Parkinson, 1982). While the everyday memory test did contain some aspects of delayed memory, notably the delayed verbal memory test, performance on this test was not related to age. This finding supports the suggestion by Youngjohn and Crook (1993) that everyday memory is a relatively stable aspect of memory until old age.

9.1.3 *Hypothesis 3*

The hypothesis that the relationship between memory and HRT use would be mediated by mood was not supported in either sample. This finding is in agreement with several previous studies (Drake et al, 2000; Jacobs et al, 1998; Kimura, 1995; Phillips & Sherwin, 1992; Robinson et al, 1994; Sherwin & Phillips, 1990). This is not an unexpected result given that the participants in both samples had normal, or lower than normal, scores on the negative mood states measured. In the absence of any notable negative mood states, it is unlikely that there would be any impairment of memory function. Future research, using samples with more variance in mood states, is needed to test this hypothesis.

9.2 *Limitations*

The results of this study cannot show causality. The cross-sectional sample did not involve random assignment of HRT and it is therefore not possible to say that it was HRT that caused the differences in everyday memory. Although steps were taken to control for potentially confounding variables, it is possible that other confounds may have contributed to the HRT effect. Although the longitudinal sample provides a much higher level of control over confounding variables, the lack of a control group prevented examination of the placebo effect of HRT and the effect of second testing on the memory tests.

Another limitation of this study is that the samples may not be representative of the population of mid-life women. The samples were not randomly selected, rather they were recruited through medical practitioners or newspaper advertisements. It is likely

therefore that women who were concerned about their memory may be over-represented in the samples. Alternatively, bearing in mind that 70% of women in English speaking countries experience no troublesome symptoms during menopause (Barrett-Connor, 1998) and do not need HRT, it is possible that these women were over-represented in the cross-sectional sample, volunteering to demonstrate that menopause does not interfere with their functioning. Also, although the mean IQ scores for both samples were only slightly above average, the generalisability of the findings of the cross-sectional sample may be limited by the high percentage of women with more than 13 years of education. It should also be noted that these results cannot be generalised to mid-life women suffering from psychological disturbance.

As previously discussed, the measurement of stressful life events and the use of a stress change score in the longitudinal sample may not be an accurate assessment of this construct. Also, the aforementioned limitations of the RBMT-E bring into question its utility as an overall measure of everyday memory in the present study.

9.3 *Implications for future research*

Although the design of this study limits the drawing of definitive conclusions about the relationships between HRT use, mood and everyday memory, it does provide grounds for future research. Replication using a random sample of mid-life women would establish the stability of the results from the cross-sectional aspect of this study. Although the longitudinal aspect of this study only set out to look at the short-term effects of HRT, it raises questions about the duration of the effect of HRT on mood. It is therefore suggested that future research should be longitudinal in design, using a large

sample, a control group, and following the women from premenopause age through well into the postmenopausal years. In this way, baseline mood and memory performance could be established, the transition through the menopause years could be monitored, and the long-term effects of HRT be examined to determine if it is protective of memory function. It is also suggested that such research be done as a joint medical/psychological academic venture so that monitoring of hormone levels and type and dosage of exogenous hormone replacement, and compliance, could be rigorously controlled.

If future research is to follow women into old age to determine the effectiveness of HRT in protecting memory function, it is important that the construct of memory adopted is appropriate for that phase of life as well as for mid-life women. Everyday memory would be a useful construct for such research because it concerns phenomena of obvious relevance to daily life (Klatzky, 1991), it is concerned with the maintenance rather than the extension of memory function (Glass, 1999), and it is a relatively stable aspect of memory in old age (Youngjohn & Crook, 1993). However, the results from the present study suggest that an overall measure of everyday memory may not be meaningful in understanding which aspects of memory are affected by HRT use. The construct of everyday memory has been criticised as ill-defined both theoretically and in terms of the cognitive mechanisms which underlie performance in real-world tasks (Puckett, Reese & Pollina, 1993). Future research is therefore needed to unravel the complexities of the construct and to determine whether it is in fact a construct in its own right or if it is simply different aspects of memory which warrant individual investigation.

The present study found the RBMT-E was well received by the participants, appeared to present adequate challenge to memory, and adapted easily to the home environment. Furthermore, Glass (1999) found that the RBMT (the original, shorter and less taxing version of the test) was a reliable and valid measure of everyday memory for older adults which predicted capacity for continued independent living and discriminated between different types of pathology underlying memory impairment. While future research is necessary to determine whether or not the RBMT-E has similar ability, it is suggested that this test, possibly in conjunction with the RBMT as everyday memory is seen to deteriorate, could be considered for use in future longitudinal studies, possibly as several tests of aspects of everyday memory rather than as an overall measure of everyday memory.

9.4 *Conclusion*

The results of this study indicate that HRT use is associated with improvement in everyday memory and that this improvement is not secondary to mood change. That improvement in mood was found in the longitudinal sample but no differences were found between the groups in the cross-sectional study supports previous findings and suggests that there is a temporary "mental tonic effect" (Utian, 1987) provided by the short-term use of HRT. The results of this study also suggest that HRT will help some women who complain of memory loss, forgetfulness, and foggy thinking during the menopause years to maintain their level of cognitive functioning and, with that, their self-confidence. Furthermore, the findings from this study indicate that, while everyday memory may be an ecologically valid construct for future research, further exploration and theorising of this construct, and its measurement, is necessary. This study therefore

contributes to the body of literature investigating the effect of HRT on cognitive function and supports the suggestion by Warga (1999) that it is the problems of memory, as experienced by women themselves, which should be examined.

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APPENDIX 1

The following press release was issued by Massey University Press Office on 27th March, 2001 with the stipulation that it was to be picked up by newspapers in the lower and central North Island only. It is known to have appeared in The Dominion and in Community papers in Wanganui and Palmerston North.

Volunteers wanted for research on menopause

Women in the prime of life are needed as volunteers for a study looking at the effects of mid-life changes and HRT use on women's memory and mood.

Virginia Bristow, a postgraduate student at Massey University, needs 150 women between the ages of 40 and 60 who are either experiencing menopause, who are about to start taking HRT, or who are already taking HRT, to participate in her study *Menopause, Mood and Memory.*

"I have interviewed women in Auckland and Christchurch and now I am looking for local women, particularly those who about to start taking HRT, to interview," Ms Bristow says. "I'm a menopause-aged women myself – a mature student – so I have some understanding of what it's like."

Participants in the study will be interviewed by Ms Bristow at their own convenience. Women who are about to start HRT will be asked to do a second interview 3 months later. Each interview takes about 45 minutes and includes measures of health, mood, and everyday memory changes. Participants' identities will be kept confidential. They will be sent a copy of the results of the study, which has approval from the Massey University Human Ethics Committee.

Any woman interested in participating can contact **Virginia Bristow** by telephoning **0800 274 536** for more information.

APPENDIX 2

- **Health professional information sheet**
- **Participant information sheet - participants recruited through health professionals.**
- **Participant information sheet – participants recruited through press release.**
- **Reply form.**
- **Consent form – participants recruited through health professionals.**
- **Consent form – participants recruited through press release.**

Massey University letter heading

1st July 2000

Health Professional Information Sheet

MENOPAUSE, MOOD AND MEMORY STUDY

Thank you for expressing your interest in collaborating in this study. My name is Virginia Bristow and I am a postgraduate student in the School of Psychology at Massey University. I am conducting this research as part of my Masters degree in Psychology under the supervision of Dr Christine Stephens. Dr Nancy Pachana is also involved in the project as an advisor on ageing and cognition.

What is the study about?
As you are aware, we are interested in investigating the cognitive and emotional sequelae of the use of hormone replacement therapy (HRT); specifically whether HRT enhances memory, and examining if there are any interaction effects of mood, concomitant medication and self-rated health.

Why are we asking for your collaboration?
We are seeking participants into the study through you for two reasons. Firstly, because the chief aim of the study is to examine the effect that HRT has on the memory and mood of the individual woman over time, both before and after she takes HRT. Secondly, because research has shown that women who present with menopause symptoms are a self-selected population who have a decreased quality of life and this is the population we are specifically interested in.

Who would we like you to approach?
The criteria for participation in the study are that the women are aged between 40 and 60 years (inclusive) and speak English or Maori. In order to have both a longitudinal and cross-section aspect to the research, we request that you invite three categories of women into the study:

- Those who are about to start taking, or thinking about taking HRT – these women will be participants for the longitudinal study and will be interviewed ***before*** they start HRT and ***again*** three months later
- Those who are already taking HRT- these women will be participants for the cross-sectional study and will be interviewed only once
- Those who are not using HRT (either through choice or for medical reasons). These participants would also be part of the cross-sectional study and will be interviewed only once.

What would we like you to do?
Once you have introduced patients into the study, we request that you give one of the "Menopause, Mood and Memory" envelopes supplied to you by the researcher to each woman who expresses an interest in participation. The envelope contains an information sheet, reply form and free-post envelope. Copies of this literature are available in Maori from the researcher if you require them. Any further action toward participation will be up to the women themselves. The *voluntary* nature of participation is strongly emphasised.

We would also request that, for the women who are about to start taking HRT, you inform them that there will be a delay in starting the medication regime as they will be requested to undergo the initial testing procedure first. Although it will be endeavoured to keep this delay to two or three days maximum, it is requested that you discuss the implications of the delay with your patient.

Research procedure to be conducted by the researcher

Participants will be interviewed in their own homes at times convenient to them. The interview will take about one hour and includes a questionnaire relating to demographic, health, lifestyle, mood and current medication information. There will also be practical tests of everyday memory. All of the measures used are standardised and reliable assessment tools which have been shown to be valid for New Zealand populations. Testing in Maori is available and will be conducted by a Maori speaker.

What will happen to the information?

The results of this research will be used for my Masters thesis and may be published in medical and/or psychological journals. A copy of any papers which result from this research will be sent to you if you wish and a summary of the results will be made available to you and the participants. Your identity, and that of the participants, will be protected throughout the study. No names will be linked to the results and no individual results will be studied or reported. Only Dr. Stephens and myself will have access to the study material and it will be kept in a secure place until the end of the study, at which time all the contact information will be destroyed.

While your collaboration is very much appreciated, you are free to withdraw from the study at any time. If you wish to contact Dr Stephens or myself at any time during the study please do so by writing to the above address or by telephoning or emailing the numbers given below.

Virginia Bristow
Masterate Student
Ph. (06) 350 5874
Email: vbristow@clear.net.nz

Dr Christine Stephens
Lecturer
Ph. (06) 350 5799 ext. 2071
Email: C.V.Stephens@massey.ac.nz

Massey University letter heading

1 July, 2000

Information Sheet

MENOPAUSE, MOOD AND MEMORY STUDY

You are invited to take part in a study about memory and mood in mid-life women. You can choose whether or not to take part, and can take as long as you wish to decide. This information sheet has come to you through your doctor who is assisting with the research by introducing women to the study.

My name is Virginia Bristow and I am a postgraduate student in the School of Psychology at Massey University. I am conducting this research as part of my Masters degree in Psychology under the supervision of Dr. Christine Stephens.

What is the study about?
As your doctor may have mentioned to you, there is some evidence that hormone changes at mid-life affect women's memory and mood, and the purpose of this study is to understand more about these effects.

Am I eligible to take part?
If you wish to take part in the study you should be aged between 40 and 60 years (inclusive). We are looking for 150 women who fit into one of three different groups:

1. Women who are about to start taking, or thinking about taking hormone replacement therapy (HRT).
2. Women who are already taking HRT
3. Women who are not using HRT

What will participants do?
If you fit into Group 1 above, you are about to start taking, or thinking about taking HRT, you will be asked to do **TWO** interviews with me. The first will be ***before*** you start taking HRT and the second will be ***after*** you have been on HRT for three months. Each interview will take about one hour and take place in your own home at a time convenient to you. The interview involves filling in a questionnaire about yourself, your health and wellbeing, and taking some practical everyday memory tests. Both interviews are structured in the same way although some of the memory tests will be slightly different on the second interview.

If you fit into Group 2 (you are already taking HRT) or Group 3 (you are not using HRT either because you do not want to or for medical reasons) you will be asked to do **ONE**

interview with me in your own home at a time convenient to you. This interview will take about one hour and involve filling in a questionnaire about yourself, your health and wellbeing, and taking some practical everyday memory tests.

The interviews can be conducted in English or Maori, whichever you prefer.

What will happen to the information?
The results of the study will be used for my Masters thesis and may be published in medical or psychological journals. A summary of the results will be made available to every participant. However, if you take part, your identity will be protected throughout the study. No names will be linked to the results and no individual results will be studied or reported. Only myself, Dr. Stephens, and Dr Nancy Pachana (who is also part of the research team) will have access to the study material and it will be kept in a secure place until the end of the study, at which time all the contact information that we receive (names and addresses) will be destroyed.

Summary of your rights

If you choose to participate in the study, and please remember that this must be *your* choice, you have the right to:

- refuse to answer any particular questions
- withdraw from the study at any time
- participate in the study anonymously knowing that your personal details are confidential
- contact the researcher or her supervisor at any time during the study
- receive information about the results at the end of the study.

If you have any queries or concerns about your rights as a participant in this study, you may wish to contact a Health and Disability Advocate, telephone: 0800 205 555 (Northland down to Franklin District); 0800 423 638 (rest of North Island down to Wellington); 03 377 7501 (Christchurch); 0800 37 77 66 (rest of South Island).

This study has received ethical approval from the Manawatu-Whanganui Ethics Committee on behalf of Auckland/North, Bay of Plenty, Canterbury and Otago.

If you are interested in taking part in the study, please complete the enclosed Reply Form and return it to me in the free post envelope provided. Replying at this point does not oblige you to take part. You can contact myself, Dr Stephens or Dr Pachana by writing to the address above, or by telephoning us on **0800 274 536** or **(06) 350 5874**.

Thank you for giving this information your consideration.

Massey University letter heading

1st February 2001

Information Sheet

MENOPAUSE, MOOD AND MEMORY STUDY

My name is Virginia Bristow and I am a postgraduate student in the School of Psychology at Massey University. I am conducting this research as part of my Masters degree in Psychology under the supervision of Dr. Christine Stephens.

What is the study about?
There is some evidence that hormone changes at mid-life affect women's memory and mood, and the purpose of this study is to understand more about these effects.

Am I eligible to take part?
If you wish to take part in the study you should be aged between 40 and 60 years (inclusive). We are looking for 150 women who fit into one of three different groups:

4. Women who are about to start taking, or thinking about taking hormone replacement therapy (HRT).
5. Women who are already taking HRT
6. Women who are not using HRT

What will participants do?
If you fit into Group 1 above, you are about to start taking, or thinking about taking HRT, you will be asked to do **TWO** interviews with me. The first will be ***before*** you start taking HRT and the second will be ***after*** you have been on HRT for three months. Each interview will take about 45 minutes and take place in your own home at a time convenient to you. The interview involves filling in a questionnaire about yourself, your health and wellbeing, and taking some practical everyday memory tests. Both interviews are structured in the same way although some of the memory tests will be slightly different on the second interview.

If you fit into Group 2 (you are already taking HRT) or Group 3 (you are not using HRT either because you do not want to or for medical reasons) you will be asked to do **ONE** interview with me in your own home at a time convenient to you. This interview will take about 45 minutes and involve filling in a questionnaire about yourself, your health and wellbeing, and taking some practical everyday memory tests.

The interviews can be conducted in English or Maori, whichever you prefer.

What will happen to the information?
The results of the study will be used for my Masters thesis and may be published in medical or psychological journals. A summary of the results will be made available to every participant. However, if you take part, your identity will be protected throughout the study. No names will be linked to the results and no individual results will be studied or reported. Only myself and Dr. Stephens will have access to the study material and it will be kept in a secure place until the end of the study, at which time all the contact information that we receive (names and addresses) will be destroyed.

Summary of your rights

If you choose to participate in the study you have the right to:

- refuse to answer any particular questions
- withdraw from the study at any time
- participate in the study anonymously knowing that your personal details are confidential
- contact the researcher or her supervisor at any time during the study
- receive information about the results at the end of the study.

If you have any queries or concerns about your rights as a participant in this study, you may wish to contact a Health and Disability Advocate, telephone: 0800 205 555 (Northland down to Franklin District); 0800 423 638 (rest of North Island down to Wellington); 03 377 7501 (Christchurch); 0800 37 77 66 (rest of South Island).

This study has received ethical approval from the Massey University Human Ethics Committee and from the Manawatu-Whanganui Ethics Committee on behalf of Auckland/North, Bay of Plenty, Canterbury and Otago.

If you are interested in taking part in the study, please complete the enclosed Reply Form and return it to me in the free post envelope provided. Replying at this point does not oblige you to take part. You can contact myself or Dr Stephens by writing to the address above, or by telephoning us on **0800 274 536** or **(06) 350 5874**.

Thank you for giving this information your consideration.

Massey University letter heading

Reply Form

MENOPAUSE, MOOD AND MEMORY STUDY

I have read the information sheet about the Menopause, Mood and Memory Study and I am interested in participating and being interviewed in my own home.

Which group do you fit into? *Please tick the appropriate box*

About to start taking, or thinking about taking HRT .... ☐
Already taking HRT ..... ☐
Not using HRT..... ☐

In which language would you like the interview(s) to be conducted?
Please tick the appropriate box

English . . . . . ☐
Maori . . . . . ☐

Do you have any regular times that would suit you best for interviews?
Please indicate what these times are

.....

Please provide us with your contact details:

Name: .....

Address: .....

Phone number: .....

Signed: .....

Thank you for your interest. If you have any questions about this form please phone the researcher, Virginia Bristow, on **0800 274 536** or **(06) 350 5874**.

Remember to use the **free post** envelope to return this form. You don't need to use a stamp.

Massey University letter heading

Consent Form

MENOPAUSE, MOOD AND MEMORY STUDY

I have read and I understand the information sheet dated 20 March 2000 for volunteers taking part in the study about the effects of hormone change on memory and mood in mid-life women. I have had time to consider whether to take part. My questions have been answered to my satisfaction and I know who to contact if I have any further questions about the study.

I understand that, although my doctor invited me into this study, taking part is voluntary (my choice). I understand that I may withdraw from the study at any time and decline to answer any particular questions and that this will in no way affect my future health care.

I understand that participation in this study is confidential and that no material which could identify me will be used in any reports or publications arising from this research. I also understand that the researcher will not communicate with my doctor about my participation in this research or the results of the testing.

I wish to receive a copy of the results of this study: ☐ yes
☐ no

I .....(full name) hereby consent to take part in this study.

Signature ..... Date .....

Researcher:
Virginia Bristow
Ph. 06 350 5874

Supervisor:
Dr Christine Stephens
Ph. 06 350 5700 ext. 2071

Massey University letter heading

Consent Form

MENOPAUSE, MOOD AND MEMORY STUDY

I have read and I understand the information sheet dated 1st February 2001for volunteers taking part in the study about the effects of hormone change on memory and mood in mid-life women. I have had time to consider whether to take part. My questions have been answered to my satisfaction and I know who to contact if I have any further questions about the study.

I understand that I may withdraw from the study at any time and decline to answer any particular questions.

I understand that participation in this study is confidential and that no material which could identify me will be used in any reports or publications arising from this research.

I wish to receive a copy of the results of this study: ☐ yes
☐ no

I .....(full name) hereby consent to take part in this study.

Signature ..... Date .....

Researcher:
Virginia Bristow
Ph. 06 350 5874

Supervisor:
Dr Christine Stephens
Ph. 06 350 5700 ext. 2071

APPENDIX 3

- **Demographic questionnaire**
- **Positive and Negative Affect Schedule (PANAS)/Profile of Mood States (POMS)**
- **Digit Span**
- **National Adult Reading Test (NART)**
- **Rivermead Behavioural Memory Test – Extended Version (RBMT-E)**
- **Women's Health Questionnaire**

MENOPAUSE, MOOD & MEMORY

1. Which of the following best describes your present work situation? (*please tick one box*)

- ☐ full-time paid work (30 hours a week or more)
- ☐ part-time paid work (less than 30 hours a week)
- ☐ unpaid work in the home
- ☐ unemployed/redundant
- ☐ retired or permanently unable to work
- ☐ other (please specify): _____

2. Please indicate the highest level of education you have completed. *(please tick one box)*

- ☐ primary school
- ☐ some secondary school
- ☐ School Certificate, University Entrance or Bursary
- ☐ Tertiary qualification

3. Which ethnic group do you feel you most belong to? *(please tick one box)*

- ☐ NZ European
- ☐ NZ Maori
- ☐ Pacific Islander
- ☐ Asian
- ☐ European
- ☐ Other (please specify): _____

4. What is your age in years? ☐☐

5. Do you engage in moderate exercise for at least 30 minutes, at least 3 times a week?

- ☐ yes
- ☐ no

6. Are you right-handed or left-handed?

- ☐ right-handed
- ☐ left-handed
- ☐ ambidextrous

7. Have you ever been knocked unconscious or concussed?

- ☐ yes
- ☐ no

8. Over the past 12 months, would you say your health has been:
(please tick one box)

- ☐ very good
- ☐ good
- ☐ fair
- ☐ poor
- ☐ very poor

9. Do you have a **family** history of any of the following neurological conditions?
(please tick all that apply)

- ☐ strokes or TIA's
- ☐ Alzheimer's Disease
- ☐ another type of dementia
- ☐ don't know

10. Do you have a history of smoking?

- ☐ never smoked
- ☐ past smoker
- ☐ current smoker

11. Do you have a history of any of the following?
(please tick all that apply)

- ☐ diabetes
- ☐ high blood pressure
- ☐ heart disease
- ☐ epilepsy
- ☐ cancer
- ☐ depression
- ☐ pre-menstrual tension

12. Have you had any of the following operations?
(please tick all that apply)

- ☐ hysterectomy (removal of uterus/womb)
- ☐ removal of **one** ovary
- ☐ removal of **both** ovaries

13. If you have not had a hysterectomy or any ovarian surgery, have you had a menstrual period in the last 12 months?

- ☐ yes
- ☐ no

14. If 'yes' to Q13, have your periods been regular during the past 12 months?

☐ yes
☐ no

15. Are you currently taking any hormone replacement medication, from your doctor, chemist or health store? *(if yes, please list)*

☐ yes _____
☐ no

16. Are you currently taking any other medications, either prescribed or regularly taken over-the-counter preparations? *(if yes, please list)*

☐ yes _____

_____

_____

_____

☐ no

17. I am now going to ask you about areas of your life in which you may have experienced some stress over the **past year**. Please look at this card (*show card and code the responses directly into boxes)* and tell me which statement most closely reflects how stressful each area has been for you.

No, not at all	**No, not much**	**Yes, sometimes**	**Yes, definitely**
0	**1**	**2**	**3**
Family			
Close friends			
Love and relationships			
Work			
Financial			
Victim of crime			
Other personal areas of life			

This scale consists of a number of words that describe different feelings and emotions. Please read each item carefully. Then choose **ONE** number from the following five point scale which best describes **how you have been feeling during the past week including today** and write it beside the word:

Office use only

1 very slightly or not at all	2 a little	3 moderately	4 quite a bit	5 extremely

Cols 37 38 39

Interested	____	Irritable	____	Distressed	____
Alert	____	Excited	____	Ashamed	____
Upset	____	Inspired	____	Strong	____
Nervous	____	Guilty	____	Determined	____
Scared	____	Attentive	____	Hostile	____
Jittery	____	Enthusiastic	____	Active	____
Proud	____	Afraid	____	Gloomy	____
Friendly	____	Unworthy	____	Desperate	____
Tense	____	Spiteful	____	Sluggish	____
Angry	____	Sympathetic	____	Rebellious	____
Worn out	____	Uneasy	____	Helpless	____
Unhappy	____	Restless	____	Weary	____
Clear-headed	____	Unable to concentrate	____	Bewildered	____
Lively	____	Fatigued	____	Alert	____
Confused	____	Helpful	____	Deceived	____
Annoyed	____	Sorry for things done	____	Furious	____
Shaky	____	Discouraged	____	Efficient	____
Listless	____	Resentful	____	Trusting	____
Peeved	____	Nervous	____	Full of pep	____
Considerate	____	Lonely	____	Bad-tempered	____
Sad	____	Miserable	____	Worthless	____
Active	____	Muddled	____	Forgetful	____
On edge	____	Cheerful	____	Carefree	____
Grouchy	____	Bitter	____	Terrified	____
Blue	____	Exhausted	____	Guilty	____
Energetic	____	Anxious	____	Vigorous	____
Panicky	____	Ready to fight	____	Hopeless	____
Relaxed	____	Uncertain about things	____	Bushed	____
Good natured	____				

79 80 1

41

11. Digit Span (Optional)

DISCONTINUE RULE:
After scores of 0 on both trials of any item.
For both Digits Forward & Backward, administer both trials of each item even if Trial 1 is passed.

RECORDING:
All responses verbatim

SCORING RULE:
0–1 pt. for each response

Digits Forward

Item/Trial		Response	Score 0 or 1
1.	Trial 1	1 – 7	
	Trial 2	6 – 3	
2.	Trial 1	5 – 8 – 2	
	Trial 2	6 – 9 – 4	
3.	Trial 1	6 – 4 – 3 – 9	
	Trial 2	7 – 2 – 8 – 6	
4.	Trial 1	4 – 2 – 7 – 3 – 1	
	Trial 2	7 – 5 – 8 – 3 – 6	
5.	Trial 1	6 – 1 – 9 – 4 – 7 – 3	
	Trial 2	3 – 9 – 2 – 4 – 8 – 7	
6.	Trial 1	5 – 9 – 1 – 7 – 4 – 2 – 8	
	Trial 2	4 – 1 – 7 – 9 – 3 – 8 – 6	
7.	Trial 1	5 – 8 – 1 – 9 – 2 – 6 – 4 – 7	
	Trial 2	3 – 8 – 2 – 9 – 5 – 1 – 7 – 4	
8.	Trial 1	2 – 7 – 5 – 8 – 6 – 2 – 5 – 8 – 4	
	Trial 2	7 – 1 – 3 – 9 – 4 – 2 – 5 – 6 – 8	

Forward Total Score
Range = 0 to 16 ____

Digits Backward

Item/Trial		(Correct Response)/Response	Score 0 or 1
1.	Trial 1	2 – 4 (4 – 2)	
	Trial 2	5 – 7 (7 – 5)	
2.	Trial 1	6 – 2 – 9 (9 – 2 – 6)	
	Trial 2	4 – 1 – 5 (5 – 1 – 4)	
3.	Trial 1	3 – 2 – 7 – 9 (9 – 7 – 2 – 3)	
	Trial 2	4 – 9 – 6 – 8 (8 – 6 – 9 – 4)	
4.	Trial 1	1 – 5 – 2 – 8 – 6 (6 – 8 – 2 – 5 – 1)	
	Trial 2	6 – 1 – 8 – 4 – 3 (3 – 4 – 8 – 1 – 6)	
5.	Trial 1	5 – 3 – 9 – 4 – 1 – 8 (8 – 1 – 4 – 9 – 3 – 5)	
	Trial 2	7 – 2 – 4 – 8 – 5 – 6 (6 – 5 – 8 – 4 – 2 – 7)	
6.	Trial 1	8 – 1 – 2 – 9 – 3 – 6 – 5 (5 – 6 – 3 – 9 – 2 – 1 – 8)	
	Trial 2	4 – 7 – 3 – 9 – 1 – 2 – 8 (8 – 2 – 1 – 9 – 3 – 7 – 4)	
7.	Trial 1	9 – 4 – 3 – 7 – 6 – 2 – 5 – 8 (8 – 5 – 2 – 6 – 7 – 3 – 4 – 9)	
	Trial 2	7 – 2 – 8 – 1 – 9 – 6 – 5 – 3 (3 – 5 – 6 – 9 – 1 – 8 – 2 – 7)	

Backward Total Score
Range = 0 to 14 ____

Total Score
Range = 0 to 30 ____

(Sum Forward Total Score & Backward Total Score)

National Adult Reading Test (NART)

SECOND EDITION

Answer/Record Sheet

Name:..... Date of test:.....

	Errors		Errors
CHORD		SUPERFLUOUS	
ACHE		SIMILE	
DEPOT		BANAL	
AISLE		QUADRUPED	
BOUQUET		CELLIST	
PSALM		FACADE	
CAPON		ZEALOT	
DENY		DRACHM	
NAUSEA		AEON	
DEBT		PLACEBO	
COURTEOUS		ABSTEMIOUS	
RAREFY		DETENTE	
EQUIVOCAL		IDYLL	
NAIVE		PUERPERAL	
CATACOMB		AVER	
GAOLED		GAUCHE	
THYME		TOPIARY	
HEIR		LEVIATHAN	
RADIX		BEATIFY	
ASSIGNATE		PRELATE	
HIATUS		SIDEREAL	
SUBTLE		DEMESNE	
PROCREATE		SYNCOPE	
GIST		LABILE	
GOUGE		CAMPANILE	

TVTC
Thames Valley Test Company

The Rivermead Behavioural Memory Test
– Extended Version

Procedural Guide and Scoring Sheet

Subject and test details

Name

Date of birth

Date of test

Assessment ☐ First ☐ Second

Version ☐ 1 ☐ 2

Note: Before you start the test ensure you have all the appropriate equipment: test materials book and large picture card for Version 1 or 2; timer/alarm; message envelope and book; stopwatch.

1 & 2 First and Second Names

Action: Present three photographic portraits and the first and second names of the people portrayed as described in the test materials.

3 Belongings

Action: Hide two belongings as described in the test materials.

4 Appointments

Action: Demonstrate and set the timer/alarm for about 20 minutes as described in the test materials, and state questions to be asked.

5 Picture Recognition

Action: Present large picture card as described in the test materials.

6 Story (immediate)

Action: Read the story as described in the test materials, and then ask the subject to recall it.

Response: Tick each of the 21 'ideas' correctly or partially recalled.

Correctly recalled	Partially recalled (tick)	Version 2
Version 1		
Mr Brian	☐	☐ Two hundred men
Kelly	☐	☐ at a shipyard
a Security Express employee	☐	☐ on Tyneside
was shot dead	☐	☐ went on strike
on Monday	☐	☐ this morning.
during a bank raid	☐	☐ The men walked out
in Brighton.	☐	☐ over a dispute
The four raiders	☐	☐ concerning 50
all wore masks	☐	☐ redundancies.
and one carried	☐	☐ The shop steward
a sawn-off	☐	☐ Mr Thomas
shotgun.	☐	☐ Lindsay
Police detectives	☐	☐ told reporters
were sifting through	☐	☐ 'It is outrageous!
eye-witness accounts	☐	☐ The company has full order books
last night.	☐	☐ for the next two years.'
A police spokesman said	☐	☐ A management spokesperson said
'He was a very brave man.	☐	☐ 'We are hoping to begin
He went for	☐	☐ fresh negotiations
the armed raider	☐	☐ at head office
and put up a hell of a fight.'	☐	☐ tomorrow.'

Raw score

☐ Each 'idea' recalled word-perfect or using a close synonyn

☐ Each 'idea' partially recalled or recalled with an approximate synonym = ½

☐ **Total raw score** (max = 21)

Profile score conversion table					Profile score =
Predicted (premorbid) intellectual band	Profile score 0	1	2	3	
Below average	0	1	2–6	7–12	13-
Average	0–2	3–6	7–11	12–15	16-
Above average	0–4	5–9	10–13	14–17	18-

5 Picture Recognition

Action: Present picture cards as described in the test materials

Response: Record the correct identifications and the number false positives.

Version 1		Version 2
horse	☐	elephant
clock	☐	wheel
pan	☐	trumpet
racket	☐	motorbike
book	☐	tree
camel	☐	aeroplane
drum	☐	axe
pig	☐	bottle
star	☐	cake
cup	☐	watering can
table	☐	hat
ball	☐	chair
cow	☐	dustbin
kettle	☐	apple
tortoise	☐	pram
rabbit	☐	helicopter
pipe	☐	record player
watch	☐	button
bus	☐	bicycle
bell	☐	cockerel

record false positives here ☐☐☐☐☐ ☐☐☐☐[

☐☐☐☐☐ ☐☐☐☐[

Raw score

☐ Each picture correctly identified

— ☐ Deduct the number of false positives

☐ **Total raw score** (max = 20)

Profile score conversion table					Profile score =
	Profile score 0	1	2	3	4
Raw score	0–7	8–11	12–15	16–19	20

7 Face Recognition

Action: Present faces as described in the test materials.

8 Route & 9 Messages (immediate)

Action: Demonstrate the route, leaving message envelope and book at appropriate locations, as described in the test materials (Adapt the instructions to suit the room if appropriate, and no your route in the column headed 'Your own version' below.)

Response: Record the route taken by the subject and tick message/book boxes as appropriate.

	spontaneously	after prompt
Message picked up	☐	☐
Book picked up	☐	☐

Version 1	Version 2	Your own version	Subject's route
Chair 1	Heater	.....	
Door	Chair 1	.....	
Chair 2	Noticeboard	.....	
Message left at correct location			☐
Window	Table	.....	
Heater	Door	.....	
Table	Chair 2	.....	
Book left at correct location			☐
Noticeboard	Window	.....	

Scoring for Route

Raw score

If the route is completed correctly = 15

If the route is **not** completed correctly calculate the raw score:

☐ 1 Score 1 for each correct location visited regardless of order (max = 7)

☐ 2 Score 1 if the starting place was correct and score 1 if the finishing point was correct (max = 2)

☐ 3 Consider each location in turn together with the location following it, and score 1 if that particular pair order appears somewhere in the correct route list (max = 6)

Note: the last location in the sequence is not counted since there is no location following it.

Note also: If the **same** correct pair order occurs twice (or more) it should only be counted once.

— ☐ 4 Deduct 1 for every incorrect or repeated stage (i.e. a totally different location, or the same location visited more than once)

☐ **Total raw score** (max = 15)

Profile score conversion table — Profile score =

		Profile score				
Version	Age	0	1	2	3	4
1	Below 30 years	0–10	11–12	13	14	15
	30–50 years	0–8	9–11	12–13	14	15
	51 years & over	0–3	4–9	10–13	14	15
2	Below 30 years	0–6	7–10	11–13	14	15
	30–50 years	0–7	8–10	11–13	14	15
	51 years & over	0–4	5–9	10–13	14	15

Scoring for Messages

Raw score

☐ Message picked up spontaneously = 2 / with prompt = 1

☐ Book picked up spontaneously = 2 / with prompt = 1

☐ Message left in correct location = 1

☐ Book left in correct location = 1

☐ **Total raw score** (max = 6)

Profile score conversion table — Profile score =

	Profile score				
	0	1	2	3	4
Raw score	0–2	3	4	5	6

7 Face Recognition

Action: Present face cards as described in the test materials.

Response: Record the correct identifications and the number false positives.

Version 1		Version 2
p.127	☐	p.127
p.131	☐	p.131
p.137	☐	p.137
p.139	☐	p.139
p.141	☐	p.145
p.147	☐	p.149
p.149	☐	p.155
p.157	☐	p.157
p.159	☐	p.159
p.165	☐	p.165
p.169	☐	p.167
p.171	☐	p.175
p.177	☐	p.177
p.183	☐	p.183
p.185	☐	p.185

record false positives here

☐☐☐☐☐ ☐☐☐☐☐

☐☐☐☐☐

Raw score

☐ Each picture correctly identified

— ☐ Deduct the number of false positives

☐ **Total raw score** (max = 15)

Profile score conversion table — Profile score =

	Profile score				
	0	1	2	3	4
Raw score	0–9	10–11	12–13	14	15

10 Orientation & 11 Date

Action: Ask the 13 questions as described in the test materials.

Response: Record the subject's responses below.

Question/response		Raw score
1 **Year**		
1 point if correct		
2 **Month**		
1 point if correct		
3 **Day**		
1 point if correct		
4 **Time**		
1 point if within half-an-hour of correct time		
5 **Date**		
2 points if correct, 1 point if one day out		
6 **Place**		
1 point for correct name of hospital or centre, or for number of house **and** street name 0 points for 'a hospital'		
7 **City/town**		
1 point if correct (or nearest city/town if necessary)		
8 **Age**		
1 point if correct		
9 **Birth year**		
1 point if correct		
10 **Prime Minister/Governor**		
1 point if first and second names correct ½ point for correct surname only		
11 **Previous Prime Minister/Governor**		
1 point if first and second names correct ½ point for correct surname only		

12 President

1 point if first and second names correct
½ point for correct surname only

13 Previous President

1 point if first and second names correct
½ point for correct surname only

Total raw score (max = 14)

Profile score conversion table Profile score =

	Profile score				
	0	1	2	3	4
Raw score	0–10	11	12	13	14

4 Appointments

Action: Engage the subject in conversation until the alarm sounds. Prompt the subject for the two questions if not asked spontaneously.

Response

	spontaneously	after prompt
Question 1 asked	☐	☐
Question 2 asked	☐	☐

Raw score

Calculate raw score as follows:

- Each question asked spontaneously = 2
- Each question asked after prompt = 1
- Subject remembers two things had to be done but not what they were = 2
- Subject remembers one thing had to be done but not what it was = 1

☐ **Total raw score** (max = 4)

Calculate profile score later: add raw score to 'Belongings' score

6 Story (delayed)

Action: Ask the subject to recall the story again as described in the test materials.

Response: Tick each of the 21 'ideas' correctly or partially recalled.

Correctly recalled	Partially recalled (tick)	
Version 1		**Version 2**
Mr Brian	☐ ☐	Two hundred men
Kelly	☐ ☐	at a shipyard
a Security Express employee	☐ ☐	on Tyneside
was shot dead	☐ ☐	went on strike
on Monday	☐ ☐	this morning.
during a bank raid	☐ ☐	The men walked out
in Brighton.	☐ ☐	over a dispute
The four raiders	☐ ☐	concerning 50
all wore masks	☐ ☐	redundancies.
and one carried	☐ ☐	The shop steward
a sawn-off	☐ ☐	Mr Thomas
shotgun.	☐ ☐	Lindsay
Police detectives	☐ ☐	told reporters
were sifting through	☐ ☐	'It is outrageous!
eye-witness accounts	☐ ☐	The company has full order books
last night.	☐ ☐	for the next two years.'
A police spokesman said	☐ ☐	A management spokesperson said
'He was a very brave man.	☐ ☐	'We are hoping to begin
He went for	☐ ☐	fresh negotiations
the armed raider	☐ ☐	at head office
and put up a hell of a fight.'	☐ ☐	tomorrow.'

Raw score

☐ Each 'idea' recalled word-perfect or using a close synonym = 1

☐ Each 'idea' partially recalled or recalled with an approximate synonym = ½

— ☐ Subtract 1 point if the subject needed an opening prompt

☐ **Total raw score** (max = 21)

Profile score conversion table Profile score =

Predicted (premorbid) intellectual band	Profile score 0	1	2	3	
Below average	0	1–2	3–6	7–10	1
Average	0–1	2–5	6–10	11–14	1
Above average	0–3	4–7	8–12	13–15	1

8 Route & 9 Messages (delayed)

Action: Ask the subject to take the route again as described i test materials. (Adapt the instructions to suit the room if appropriate, and note your route in the column headed 'You own version' below.)

Response: Record the route taken by the subject and tick message/book boxes as appropriate.

	spontaneously	after prompt
Message picked up	☐	☐
Book picked up	☐	☐

Version 1	Version 2	Your own version	Subject's rou
Chair 1	Heater	.....	
Door	Chair 1	.....	
Chair 2	Noticeboard	.....	
Message left at correct location			☐
Window	Table	.....	
Heater	Door	.....	
Table	Chair 2	.....	
Book left at correct location			☐
Noticeboard	Window	.....	

Scoring for Route

Raw score

If the route is completed correctly = 15

If the route is **not** completed correctly calculate the raw score follows:

☐ 1 Score 1 for each correct location visited regardles order (max = 7)

☐ 2 Score 1 if the starting place was correct and score 1 the finishing point was correct (max = 2)

☐ 3 Consider each location in turn together with the location following it, and score 1 if that particular order appears somewhere in the correct route list (max = 6)
Note: the last location in the sequence is not coun since there is no location following it.
Note also: If the **same** correct pair order occurs t (or more) it should only be counted once.

— ☐ 4 Deduct 1 for every incorrect or repeated stage (i. totally different location, or the same location vis more than once)

☐ **Total raw score** (max = 15)

Profile score conversion table		Profile score =				
		Profile score				
Version	Age	0	1	2	3	4
1	Below 30 years	0–8	9–11	12–13	14	15
	30–50 years	0–6	7–10	11–13	14	15
	51 years & over	0–6	7–9	10–12	13	14–15
2	Below 30 years	0–3	4–10	11–13	14	15
	30–50 years	0–3	4–9	10–13	14	15
	51 years & over	0–6	7–9	10–11	12–13	14–15

Scoring for Messages

Raw score

☐ Message picked up spontaneously = 2 / with prompt = 1

☐ Book picked up spontaneously = 2 / with prompt = 1

☐ Message left in correct location = 1

☐ Book left in correct location = 1

☐ **Total raw score** (max = 6)

Profile score conversion table	Profile score =				
	Profile score				
	0	1	2	3	4
Raw score	0–2	3	4	5	6

1 & 2 First and Second Names

Action: Re-present the three photographic portraits and ask for the names of the people portrayed as described in the test materials.

Response

	spontaneously	after prompt
Portrait 1		
First name recalled	☐	☐
Second name recalled	☐	☐
Portrait 2		
First name recalled	☐	☐
Second name recalled	☐	☐
Portrait 3		
First name recalled	☐	☐
Second name recalled	☐	☐

Scoring for First Names

Raw score

Calculate raw score as follows:

- Each first name recalled spontaneously = 2
- Each first name recalled after prompt = 1

☐ **Total raw score** (max = 6)

Profile score conversion table		Profile score =				
Predicted (premorbid) intellectual band	Profile score 0	1	2	3	4
Below average	0	1	2–3	4	5–6
Average	0	1–2	3–4	5	6
Above average	0–1	2–3	4	5	6

Scoring for Second Names

Raw score

Calculate raw score as follows:

- Each second name recalled spontaneously = 2
- Each second name recalled after prompt = 1

☐ **Total raw score** (max = 6)

Profile score conversion table		Profile score			
Version	Predicted (premorbid) intellectual band	0	1	2	3
1	Below average	0	1	2–3	4
	Average & above average	0–1	2	3–4	5
2	Below average	0	1	2–3	4–5
	Average & above average	0	1	2–4	5

3 Belongings

Action: Pause/prompt the subject for the hidden belongings described in the test materials.

Response

	spontaneously	after prompt
Belonging 1 recalled	☐	☐
Belonging 2 recalled	☐	☐
Location 1 recalled	☐	☐
Location 2 recalled	☐	☐

Raw score

Calculate raw score as follows:

- Each belonging recalled spontaneously = 2
- Each belonging recalled after prompt = 1
- Each location recalled spontaneously = 2
- Each location recalled after prompt = 1

☐ **Total raw score** (max = 8)

Profile score conversion table	Profile score =			
	Profile score			
	0	1	2	3
Combined raw score	0–8	9	10	11

Note: Add 'Appointments' raw score (p.3) to 'Belongings' raw score (max = 12) to obtain one combined profile score

Score summary

	Raw score	Profile score
1 First Names	☐	☐
2 Second Names	☐	☐
3 Belongings	☐ +	☐
4 Appointments	☐	☐
5 Picture Recognition	☐	☐
6 Story (immediate)	☐	☐
6 Story (delayed)	☐	☐
7 Face Recognition	☐	☐
8 Route (immediate)	☐	☐
8 Route (delayed)	☐	☐
9 Messages (immediate)	☐	☐
9 Messages (delayed)	☐	☐
10 & 11 Orientation and Date	☐	☐
Totals	☐	☐
	max = 157	max = 48

WOMEN'S HEALTH QUESTIONNAIRE

Please **indicate how you have been feeling during the past week including today** by choosing a number from the following four point scale to write beside the statement:

Office Use only

No, not at all 0	**No, not much** 1	**Yes, sometimes** 2	**Yes, definitely** 3	
_____	I wake early then sleep badly for the rest of the night			☐1
_____	I get very frightened or panic feelings for apparently no reason at all			☐2
_____	I feel miserable and sad			☐3
_____	I feel anxious when I go out of the house on my own			☐4
_____	I have lost interest in things			☐5
_____	I get palpitations or a sensation of "butterflies" in my stomach or chest			☐6
_____	I still enjoy the things I used to			☐7
_____	I feel life is not worth living			☐8
_____	I feel tense or "wound up"			☐9
_____	I have a good appetite			☐10
_____	I am restless and can't keep still			☐11
_____	I am more irritable than usual			☐12
_____	I worry about growing old			☐13
_____	I have headaches			☐14
_____	I feel more tired than usual			☐15
_____	I have dizzy spells			☐16
_____	My breasts feel tender or uncomfortable			☐17
_____	I suffer from backache/or pains in my limbs			☐18
_____	I have hot flushes			☐19
_____	I am more clumsy than usual			☐20
_____	I feel rather lively and excitable			☐21

No, not at all **0**	**No, not much** **1**	**Yes, sometimes** **2**	**Yes, definitely** **3**	Office Use only
_____	I have abdominal cramps or discomfort			☐22
_____	I feel sick or nauseous			☐23
_____	I have lost interest in sexual activity			☐24
_____	I have feelings of well-being			☐25
_____	I have heavy periods			☐26
_____	I suffer from night sweats			☐27
_____	My stomach feels bloated			☐28
_____	I have difficulty in getting off to sleep			☐29
_____	I often notice pins and needles in my hands and feet			☐30
_____	I am satisfied with my current sexual relationship *(please omit if not sexually active)*			☐31
_____	I feel physically attractive			☐32
_____	I have difficulty in concentrating			☐33
_____	As a result of vaginal dryness some sexual activity has become uncomfortable *(please omit if not sexually active)*			☐34
_____	I need to pass urine/water more frequently than usual			☐35
_____	My memory is poor			☐36

APPENDIX 4

MENOPAUSE, MOOD AND MEMORY

PILOT STUDY REPORT

Prepared by:

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Postgraduate student with the
School of Psychology
Massey University

For:

MANAWATU WHANGANUI ETHICS COMMITTEE

MAY, 2000

MENOPAUSE, MOOD AND MEMORY

PILOT STUDY REPORT

Aims: To pilot a questionnaire and battery of 'everyday memory' and 'mood' measures on a group of mid-aged volunteers to test their suitability for New Zealand women. This pilot is in preparation for a main study which will investigate the effects of hormone replacement therapy (HRT) on memory and mood in mid-life women.
Method: 34 women who responded to an advertisement in a community newspaper or heard about the study by word of mouth completed the self-administered questionnaire and underwent memory testing.
Results: It was found that several participants needed assistance with the questionnaire. The battery of 'mood' and 'everyday memory' measures was well-received.
Conclusion: The questionnaire should be revised, restructured and administered by the researcher. The 'mood' and 'everyday memory' tests are appropriate for use with mid-life New Zealand women and should be used in the main study.

There is now considerable evidence from research in the neurosciences that oestrogen influences cognitive functions associated with memory (McEwen, Alves, Bulloch & Weiland,1997). Prospective controlled studies have demonstrated that exogenous oestrogen may enhance short-term, long-term and verbal memory (Sherwin, 1997). These findings are important in the short-term for mid-life women who suffer memory problems as they go through menopause and in the long-term in relation to recent suggestions that treatment with oestrogen replacement delays the onset of dementia of the Alzheimer's type.

While menopause has been associated with disturbances of mood and behaviour by medical observers since the 18th century, research has failed to systematically link major depressive disorder with changes in hormonal status (Schmidt & Rubinow, 1991). However, research indicates that, for a minority of women, there may be a modest increase in depressive symptoms during perimenopause (Avis, Brambilla & McKinlay, 1994). While research on the effect of HRT on mood is equivocal, it does suggest that, overall, placebo-controlled trials of oestrogen replacement in naturally menopausal women without significant baseline depressive symptomatology show a beneficial effect of oestrogen on mood and sense of wellbeing (Pearlstein, Rosen & Stone, 1997).

It is well established that negative mood states are frequently associated with impairment of memory and other cognitive functions (eg Deptula, Manevitz & Yozawitz, 1991). It has also been found that aging moderates the relationship between emotional state and memory functions in that older people are more vulnerable than the young to the adverse effects of negative emotional states on memory (Deptula, Singh & Pomara, 1993). The main study for which this pilot study is being conducted will therefore investigate the main effects of HRT on both mood and memory and test the hypothesis that the enhancement of memory by oestrogen is mediated by mood.

The aims of this pilot study are to test a battery of 'everyday memory' and 'mood' measures and pretest a self-administered questionnaire. The measures have been designed overseas and their suitability for mid-life New Zealand women in terms of face validity and reliability will be assessed. The questionnaire will be assessed for comprehensibility and ambiguity.

METHOD

Participants

A sample of 34 women aged between 40 and 60 years was used to pilot test the questionnaire and battery of mood and memory measures. These women were volunteers from Christchurch and Palmerston North who responded to an advertisement placed in the 'Guardian' – a free, community newspaper circulated in the Palmerston North area (see Appendix A) or who were recruited by word of mouth. Participants chose whether to be interviewed in their own homes or at Massey University and selected the date and time. Interview time was estimated at between 45-60 minutes. Participants were invited and encouraged to make comments about any aspects of the questionnaire and test measures.

Questionnaire

The questionnaire (see Appendix B) was designed to be self-administered in the presence of the researcher. It included the following:-

Demographic information: age, level of education, employment status, current level of exercise and smoking history.

Neurological Information: handedness, head injury and family history of neurological conditions.

Gynaecological/Menopausal Status: gynaecological surgery history and menopausal status, both actual and perceived.

Medication: All current medications, including HRT, listed.

Health Information:

SF-36 Health Status Questionnaire

This measure is designed to show how individuals perceive several aspects of their state of health. It consists of 8 scales: general health, physical functioning, social functioning, role limitation due to physical problems, role limitation due to emotional problems, mental health, vitality and bodily pain. For each scale, the median of the reliability coefficients across 14 studies equalled or exceeded .76 and test-retest reliability ranged from .60 to .81. The questionnaire has good convergent, discriminant and criterion-based validity (Ware,Snow, Kosinski & Gandek, 1997). The SF-36 has been validated for English, American, Australian and New Zealand populations (Wheadon, Kokaua & Sceats, 1994).

Women's Health Questionnaire (WHQ)

The WHQ is designed specifically to study possible changes in health and well-being during the menopause transition; it is a measure of mid-aged women's perceptions of their emotional and physical health (Hunter, 1992) which has been found to be a sensitive measure of response to hormone replacement therapy (Wiklund et al, 1992). The measure can produce a total well-being score or nine subscales pertaining to depressed mood, anxiety, attractiveness, sleep, somatic, memory, vasomotor, sexual and menstrual problems. The subscales of depressed mood, anxiety and attractiveness were

not used in this study. It has good reliability and concurrent validity (Hunter, 1992; Wiklund et al, 1992).

Health conditions
The respondents were asked about their medical history with regard to health conditions which may impact on their cognitive ability or affective status.

Mood Measures:
Positive and Negative Affect Schedule (PANAS)
This mood scale is designed to measure two dominant and relatively independent dimensions of affective structure – positive affect (PA) and negative affect (NA). PA reflects the extent to which a person feels enthusiastic, active and alert. High PA is a state of high energy, full concentration and pleasurable engagement, whereas low PA is characterised by sadness and lethargy. In contrast, NA is a general dimension of subjective distress and unpleasurable engagement that subsumes a variety of aversive mood states, including anger, contempt, disgust, guilt, fear and nervousness, with low NA being a state of calmness and serenity (Watson, Clark & Tellegen, 1988).

The two 10-item 5-point adjective rating scales have high internal consistency with alpha reliabilities ranging from .86 to .90 for PA and from .84 to .87 for NA; the reliability of the scales is stable over a 2-month time period. The scales are largely uncorrelated (-.12 to -.23), have adequate test-retest reliability and high convergent and discriminant validity (Watson, Clark & Tellegen, 1988).

Profile of Mood States (POMS)
This mood scale is designed to identify and assess transient, fluctuating affective states. It measures mood changes on six affective states: tension/anxiety, depression/dejection, anger/hostility, vigor/activity, fatigue/inertia and confusion/bewilderment. A total mood disturbance score can also be obtained by summing the sub-scale scores. It has proved to be a useful descriptive measure for assessing psychiatric outpatients and assessing their responses to various therapeutic approaches. It is also recommended for experimental manipulations on normal subjects (McNair, Lorr & Droppleman, 1981).

This 65 item 5-point adjective rating scale shows high internal consistency with alpha reliabilities ranging from .84 for confusion/bewilderment to .95 for depression/ dejection. Test-retest reliability is high for a mood scale ranging from .65 for vigor/activity to .74 for depression/dejection. Factor analysis demonstrated excellent congruent validity and evidence of predictive and construct validity of the measure has been demonstrated in four areas of research (McNair, Lorr & Droppleman, 1981).

Neuropsychological Assessment:

The Rivermead Behavioural Memory Test – Extended Version RBMT-E
The original version of this test, the Rivermead Behavioural Memory Test (Wilson, Cockburn & Baddeley, 1985) was designed to assess the everyday memory deficits of people with moderate to severe brain injury. The Extended Version is a longer and

more demanding version of the RMBT which detects deficits and change in everyday memory. It consists of 11 subtests which measure different aspects of memory: long and short term memory; visual, verbal and spatial memory. These subtests assess skills such as recall of name, recall and whereabouts of a belonging, remembering to make an appointment, immediate and delayed recall of a story and a route traced around a room, recall of faces and objects, orientation and knowledge of the date (Wilson et al, 1999).

Raw scores on the 11 subtests are converted to profile scores ranging from 0 (impaired) to 4 (exceptionally good memory) summing to a total possible profile score of 48. Some of the profile scores are affected by age, IQ level or the version of the test used. There is no gender difference. The RBMT-E has high ecological and face validity. It also has high alternate-form reliability between the two parallel versions of the test. Mean scores are available for normal UK populations based on age, gender and IQ levels (Wilson et al, 1999). It is recommended by the test authors that minor changes be made to names and words in certain tests to make them relevant to the culture of the subjects.

Inter-rater reliability for the present study on RBMT-E ($r = .47$, $p>0.05$) were non-significant.

Digit Span

Digit Span is an optional subtest on theWechsler Memory Scale – Third Edition (WMS-III; Wechsler, 1997). It is designed to measure focused attention and working memory and is composed of two subtests: Digits Forward and Digits Backward which are administered independently of each other. On both tasks, the examiner reads a series of number sequences to the subject. For each Digits Forward item, the subject is required to repeat the number sequence in the same order as presented. For Digits Backwards, the subject is required to repeat the number sequence in the reverse order. There are 8 items for Digits Forward and 7 items for Digits Backward. The number of digits increases with each item; each item has 2 trials. Subjects score 1 for a correct answer and 0 for an incorrect answer on each trial. Each subtest is discontinued when the subject scores 0 on both trials of an item. A total Digit Span score is achieved by summing the subtest scores.

Digit Span has test-retest reliability of .83 and split-half internal consistency of .91 for the 45-54 age group. It has good criterion-related and construct validity with WAIS-R (Wechsler Adult Intelligence Scale – Revised) and WISC-III (Wechsler Intelligence Scale for Children – Third Edition; Wechsler, 1997). Inter-rater reliability results for the present study on Digit Span ($r = .97$, $p<.01$) were significant.

National Adult Reading Test (NART)

In addition to the memory tests, the National Adult Reading Test (NART) was administered to estimate IQ levels so that profile scores on the RBMT-E could be calculated. This test was specifically designed to provide a means of estimating the premorbid intelligence levels of adult patients suspected of suffering from intellectual deterioration. The test comprises a list of 50 words printed in order of increasing difficulty. The words are all 'irregular' with respect to the common rules of

pronunciation in order to minimise the possibility of reading by phonemic decoding rather than word recognition. The subject reads aloud down the list of words and the number of errors made is recorded. Wechsler Adult Intelligence Scale (WAIS) Full-Scale IQs can be predicted from this reading error score by inserting it into the appropriate formulae (Nelson & Willison, 1991). For the purpose of the RBMT-E, below average is a predicted IQ of less than 90; average is a predicted IQ of 90-110; above average is predicted IQ of 111 or more (Wilson et al, 1999).

The split half reliability for the NART is .93 (Nelson, 1982). Inter-rater reliabilities of .96 to.98 and test-retest reliability of .98 have also been reported. Cross validation research confirms the validity of the NART as a measure of general intelligence in the normal adult population (Nelson & Willison, 1991). Inter-rater reliability results for the present study on NART ($r = .95$, $p<.01$) were significant.

Approval for this study to be conducted was granted by Massey University Human Ethics Committee.

RESULTS

34 women were interviewed and tested. One data set was removed as the respondent was outside the required age range. The remaining 33 data sets were complete. Interview time was estimated at between 45-60 minutes but, in practice, took at least 90 minutes due to under-estimation of the length of time actually needed, assistance being sought with the questionnaire and the desire of all of the women to talk about their menopause experience.

Characteristics of respondents

The age of the respondents ranged from 42-60 years. The mean age of the group was 49.79. Demographic characteristics for ethnicity, education, employment and lifestyle are presented in Table 1. The question on education presented a problem with the trade/professional certificate or diploma category. One third of respondents placed themselves in this category but, on verbal enquiry, it was revealed that the qualification involved could be anything from a typing certificate to an overseas qualification to practice dentistry. Thus, this category did not determine level of education per se and could not be used to compare the education levels of users and non-users of HRT. There was no difference between HRT users and non-users in employment with 80% from both groups being in either full or part time paid work.

Neurological information

Eighty-eight percent of respondents were right handed; 6% were left handed and 6% were ambidextrous. Twenty-seven percent had been knocked out or concussed. Family history of neurological conditions were 27% for strokes or TIAs, 12% for Alzheimers and 6% for other dementias. One respondent who was adopted was unable to give this information – a situation not anticipated in the questionnaire. Several participants required assistance with the question pertaining to family history of neurological conditions.

Table 1 Demographic characteristics of sample

	No. of women (n = 33)	% of women
Ethnicity		
NZ European	27	81.8
NZer	3	9.1
European	2	6.1
Other	1	3.0
Education		
No school qualification	6	18.2
School certificate	6	18.2
6th Form certificate	2	6.1
Bursary/scholarship	1	3.0
Trade/professional certificate or diploma	11	33.3
Undergraduate degree or diploma	4	12.1
Postgraduate qualification	3	9.1
Employment		
Full time	11	33.3
Part time	15	45.5
Unpaid work	1	3.0
Retired/unable to work	1	3.0
Unemployed	2	6.1
Student	2	6.1
Other employment status	1	3.0
Exercise		
Regular exercise	25	75.8
No regular exercise	8	24.2
Smoking		
Never smoked	17	51.5
Past smokers	13	39.4
Current smokers	3	9.1

Gynaecological/menopausal status

Forty-eight percent of respondents had undergone hysterectomy and 9% of that group has also had one ovary removed. Of the women who had undergone hysterectomy, 31% were taking HRT and 30% of women with natural menopause were HRT users. Of the women who had not undergone hysterectomy, 46% had not had a period in the last 12 months. However, none of these women considered themselves postmenopausal; 40% saw themselves as premenopausal and 60% as menopausal. There was considerable confusion on this question as the terms were unfamiliar to many women.

Medications
Thirty percent (10)of the respondents were taking HRT. Sixty-four percent of respondents were on one medication other than HRT; 24% were on two and 3% on three medications. There was little difference between HRT users and non-users in the use of other medications.

Health Information
Table 2 shows the means, standard deviations and alpha coefficients for HRT users and non-users on the SF-36 and WHQ. These results reveal that the sample was in good overall health, had a high level of wellbeing and was not highly symptomatic with regard to complaints of menopause. Comments from participants indicated that the SF-36 was not well received. It was perceived as being too long, not really relating to health matters, and as being too subjective. The WHQ was well received by participants who related well to questions pertaining directly to their menopause experience.

Table 2 Means, standard deviations and alpha coefficients of SF-36 subscales and WHQ total score and subscales for users and non-users of HRT

	Use HRT (n = 10)	Non-users of HRT (n = 23)	Alpha coefficient
SF-36			
General health	21.24 (3.32)	20.44 (3.42)	.69
Physical functioning	27.80 (2.10)	25.65 (5.37)	.91
Social functioning	9.00 (1.49)	8.22 (1.98)	.63
Role limitation – physical	7.90 (0.32)	6.87 (1.63)	.90
Role limitation – emotional	5.70 (0.48)	5.22 (1.09)	.72
Mental health	24.70 (4.06)	22.87 (4.79)	.82
Vitality	17.80 (4.29)	16.52 (4.34)	.83
Bodily pain	10.12 (1.70)	9.31 (2.77)	.89
WHQ			
Total WHQ score	19.10 (8.35)	23.26 (11.08)	.73
Sleep problems	3.00 (1.32)	2.51 (1.98)	.47
Somatic problems	5.91 (2.29)	6.53 (4.13)	.70
Memory problems	3.55 (2.48)	5.12 (2.27)	.66
Vasomotor symptoms	0.80 (1.11)	2.04 (1.97)	.91
Sexual difficulties	1.13 (1.38)	1.42 (1.49)	.59
Menstrual problems	2.28 (2.31)	2.26 (2.19)	.70

Mood
The means, standard deviations and alpha coefficients of PANAS and POMS for users and non-users of HRT are given in Table 3. There was a significant difference between scores on the POMS subscales of 'depression' ($f(1,31) = 4.29$, $p<0.05$) and 'anger' ($f(1,31) = 6.95$, $p<0.05$) indicating lower levels of these mood states for those who use HRT. Both of these mood measures were well received by the participants, were comprehensible and easily self-administered.

Table 3 Means, standard deviations and alpha coefficients of PANAS subscales and Profile of Mood States total score and subscales for users and non-users of HRT

	Use HRT (n = 10)	Non-users of HRT (n = 33)	Alpha coefficient
PANAS			
Positive affect	29.50 (8.40)	30.57 (7.99)	.88
Negative affect	12.90 (2.51)	15.57 (5.87)	.92
POMS			
Total POMS score	42.70 (22.57)	62.70 (26.63)	.91
Tension	7.50 (5.19)	9.96 (6.83)	.89
Depression	4.60 (4.60)*	11.00 (9.23)	.93
Anger	3.00 (3.71)*	6.74 (3.76)	.90
Vigor	17.00 (7.15)	15.61 (6.27)	.85
Fatigue	7.80 (5.61)	9.65 (5.69)	.90
Confused	4.80 (3.43)	8.96 (6.22)	.90

$p<0.05$

Neurological Assessment

Rivermead Behavioural Memory Test (RBMT-E)

Table 4 shows the means and standard deviations for HRT users and non-users on the RBMT-E subscales. There were no significant differences between the groups on any of the scales.

Table 4 Means and standard deviations of RBMT-E subscales for users and non-users of HRT with comparative means from UK research

	Use HRT (n = 10)	Non-users of HRT (n = 23)	Comparative UK means age 30-50 (n = 68)	Comparative UK means age >50 (n = 53)
RBMT-E				
First names	3.50 (1.51)	3.48 (1.47)	3.32	3.32
Second names	2.80 (1.75)	3.17 (1.56)	3.49	3.30
Belongings/Appointments	10.20 (1.75)	10.26 (1.77)	10.22	9.81
Picture recognition	14.30 (3.33)	13.78 (3.38)	13.16	12.92
Story (immediate)	9.10 (3.03)	7.22 (3.59)	9.07	10.11
Story (delayed)	8.20 (3.33)	6.13 (3.61)	7.72	8.18
Face recognition	12.60 (1.58)	13.04 (2.10)	12.81	11.83
Route (immediate)	13.80 (1.40)	13.70 (1.89)	12.90	11.77
Route (delayed)	13.80 (2.10)	13.78 (1.68)	12.41	11.28
Messages (immediate)	5.90 (0.32)	5.83 (0.49)	5.68	5.57
Messages (delayed)	5.80 (0.42)	5.74 (0.69)	5.71	5.13
Orientation and date	13.20 (0.79)	12.91 (0.90)	13.01	13.15

of menopause status can be assessed by the researcher. Alteration to the questionnaire will be made accordingly to achieve a more accurate and objective assessment of menopause status.

In light of the negative feedback from participants about the SF-36 health questionnaire and its length, this measure will be replaced by a single question on self-rated health. This question, which has been found to be a significant predictor of mortality in older adults (Wolinsky & Johnson, 1992), asks participants to rate their health over the previous 12 months on a five-point scale. It is considered that this single measure of self-rated health, together with the health information from the demographic section and the WHQ will provide adequate data on health status for the main study. This change will also have the advantage of reducing the length of the questionnaire and the time taken for completion.

The WHQ and the mood measures will be self-administered and therefore separated from the demographic section of the questionnaire.

Both mood measures will be retained. The POMS measure was revealed to be a sensitive measure of mood with this group of mid-life women and supported the beneficial effect of HRT on two of the subscales of mood even on such a small sample. Although provisional analysis of the PANAS did not reveal any relationship with use of HRT in this sample, it is a short and reliable measure which targets different aspects of mood from POMS.

The two neurological tests of memory will also be retained. Although no relationship was found between HRT use and the RBMT-E in this small sample, the high ecological validity of the test, the comparability of the mean scores with the UK norms, the ease of adapting the test to different home environments, and its acceptance by participants as a face-valid test of everyday memory reinforce the utilisation of this measure.

Although the inter-rater reliability testing on the RBMT-E did not give satisfactory results, this may, to a certain extent be explained by the short time interval between testing. Two parallel versions of the test were used, one by each researcher, and these versions are very similar. For this reason, in several of the tests, it was possible that the participants retained knowledge from the first testing which confounded their results in the second. An example of this occurred in the 'face recognition' test when pictures of 15 faces were shown one at a time for 3 seconds each. After a filled delay the participant was required to select the original 15 from a set of 30. Although the faces in each version of the test were different, during the second testing some of the participants rejected faces they had just been shown on the basis that they thought they were from the previous days testing. However, there is still a strong indication that the procedures of administration and scoring of the tests were not consistent between researchers. For this reason, before the main study commences, full training will be given to both researchers to ensure that the instructions for conducting and scoring the RBMT-E, as laid out in the test manual, are strictly adhered to.

APPENDIX 5

Letter to participants with summary of results

Massey letterhead

1st February 2002

Dear

MENOPAUSE, MOOD AND MEMORY STUDY

This letter is to thank you very much for your interest and effort in participating in the above study which I undertook as part of my Masters degree in Psychology, and to let you know the results. Your participation was very much appreciated; without it the study could not have happened.

What the study was about

The aim of the study was to investigate the effects of HRT on mood and memory in mid-life women. As you are aware, at menopause we undergo big hormonal changes which result in us having less oestrogen circulating in our bodies and it is thought that it is the lower level of oestrogen which is responsible for some mood changes and memory problems which can occur. While HRT is usually prescribed to alleviate the physical symptoms of menopause (hot flushes and night sweats), it is also suggested that the oestrogen in HRT enhances mood and improves memory.

Although animal research has shown that oestrogen influences memory and enhances mood because of its influence on the brain, research on mid-life women has shown mixed results and no conclusive evidence has emerged. It has been suggested that a reason for these inconclusive results is that the research has not looked at aspects of memory which women themselves complain about during menopause and that it has concentrated on depressed mood states rather than looking at a wide range of mood states.

What the study looked at

In this study therefore, I used memory tests that were concerned with everyday memory and a mood questionnaire which contained both positive and negative mood states. Aspects of memory investigated were: everyday memory, short-term attention, and working memory. Mood states investigated were positive affect, negative affect, and mood disturbance which comprised sub-scales of: depression, anxiety, anger, vigor, friendliness, fatigue, and confusion. I collected data from two samples of women: a cross-sectional sample (124 of you who were interviewed only once) to see if there were any differences between mood and memory for HRT users and non-users, and a longitudinal sample (17 of you who were interviewed twice, once before starting HRT and again after taking HRT for 3 months) to investigate the short-term effects of HRT on mood and memory.

What did I find

Firstly, as a generalisation, both samples comprised very healthy women – both physically and psychologically.

In the cross-sectional sample no differences were found on any of the mood states between HRT users and non-users. However, HRT users did perform better on the tests of everyday memory and this effect persisted when the effects of age, IQ, and level of education were controlled for.

In the longitudinal sample it was found that HRT use reduced negative mood states and enhanced positive mood states and that this effect persisted when changes in stress, self-rated health, sleep problems, vasomotor symptoms, and exercise were controlled for. This sample also showed that everyday memory and working memory improved with HRT use when age, IQ, and education were controlled for. It was also found that the improvement in memory was not secondary to the improvement in mood.

What does this mean

- That HRT does improve memory for things like recognising faces and objects, remembering names, appointments, things you have been asked to do and information you have just heard – everyday memory.

- That mood improves when HRT is first taken but this improvement would appear to short-lived. The improvement in mood was not related to stress, health, taking exercise, sleep problems or the relief of hot flushes.

- That the improvement in memory is not related to mood.

Once again, many thanks for your assistance in this research.

Yours sincerely,

Virginia Bristow