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**The association between oestrogen, memory, cognition and mood in a
Male-To-Female Transsexual Population.**

Clare Louise Miles

Thesis submitted in fulfilment of the requirements
for the degree of Doctor of Philosophy

Department of Psychology
City University, London

December 2004.

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DECLARATION

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Abstract

Research has demonstrated that gonadal hormones, including oestrogen, can influence memory and cognitive tasks that show sex differences in animals and humans. Beneficial effects of oestrogen on mood have also been reported in postmenopausal women in association with Oestrogen Replacement Therapy (ERT). Male-to-Female (M-F) transsexuals offer one of the few opportunities for studying the effect of oestrogen and other cross-sex hormones on human cognitive function. The present research examined the effect of gonadal hormones on memory, cognition and mood in a transsexual population. The aim was to determine whether treatment with oestrogen and other cross-sex hormones would influence memory and cognitive abilities that show sex differences, such that males treated with oestrogen and other cross-sex hormones would perform more like females. We also examined the effect of such hormone treatment on mood. In an initial study (Chapter 2), M-F transsexuals undergoing oestrogen treatment for sex re-assignment scored higher on Verbal Paired Associate Learning (PAL) compared to a similar transsexual control group, awaiting oestrogen treatment. No differences between these groups were detected on a control memory task (Digit Span) or on other cognitive tasks that show sex differences, including Mental Rotations and Controlled Associations. In a second study (Chapter 3), an attempt was made to summarise the magnitude and reliability of sex differences in some of the memory tasks previously used in oestrogen and memory research. In a final study (Chapter 4), a more robust design was used to further examine the association between oestrogen, memory, cognition and mood. Additional aspects of memory function and other cognitive abilities that do and do not show sex differences were used, including verbal and visual-spatial abilities. Also, a repeated measures design was used. M-F transsexuals were tested both prior to hormone treatment and after treatment had begun. In addition, some M-F transsexuals were tested both before and during a period of hormone withdrawal prior to surgery. Findings from this study did not replicate the data from the initial study reported in Chapter 2. Few changes in memory or other aspects of cognitive performance were observed and these were not consistent in the two groups of patients. Improvements in mood were observed, particularly at the commencement of oestrogen treatment. However, this improvement could have resulted from progression in the treatment program rather than from the hormone treatment per se.

CHAPTER 1: INTRODUCTION

1.1. The study of sex differences

A wealth of research has established consistent differences between males and females in various behaviours. Although males and females do not differ in general intelligence, sex differences in specific cognitive and memory abilities have been reported. On average, males outperform females on certain tests of mathematical and visual-spatial ability, whereas females outperform males on certain tests of verbal ability (Maccoby and Jacklin, 1974; Collaer and Hines, 1995; Hyde and Linn, 1988; Voyer, Voyer and Bryden, 1995). In general these differences are reliably seen cross-culturally (Silverman, Philips and Silverman, 1996; Stage, 1988; Birenbaum, Kelley and Levi-Keren, 1994). However, this is not to suggest superiority in either gender and before reviewing this literature it is important to emphasise from the outset that these sexually dimorphic traits in cognition and memory do not negate overlap between the sexes or negate the wide variation within each sex. For example, some females may have greater visual-spatial abilities than some males. Similarly, some males may have greater verbal abilities than some females.

It has been suggested that the term 'sex' refers to biological differences between males and females and 'gender' relates to the social traits associated with being male or female (Halpern, 2000), however, for the purpose of this thesis both terms will be used interchangeably. This is because it is difficult to ascertain which sex / gender differences can be explained by biological or environmental factors. Furthermore, the term 'sexual dimorphism' will be used here to refer to forms of behaviour that on average vary according to sex.

1.2. Sex differences in cognitive and memory abilities

As previously mentioned, males outperform females on certain tests of mathematical and visual-spatial ability, such as Mental Rotation and spatial perception whereas females outperform males on certain tests of verbal ability, such as word fluency and generating synonyms (Maccoby and Jacklin, 1974; Collaer and Hines, 1995). There are also sex differences in memory, although these are not as clearly defined. Whilst females perform better on average than males on tests of verbal memory, such as Paired Associate Learning (PAL) and story recall (DesRosiers and Ivison, 1988; Ivison, 1977; Mann, Sasanuma, Sakuma and Masaki, 1990), some other

tests of verbal memory, such as Digit Span, do not show a sex difference (Blum, Fosshage and Jarvik, 1972; Chavez, Trautt, Brandon and Steyaert, 1983; Makarec and Persinger, 1993; 1995). Females may also excel at memory involving some spatial processes such as remembering the locations of objects (Silverman and Eals, 1992). However, a male advantage has been reported for retaining spatial information, such as the position of letters in a grid (Kails and Siegel, 1977), as well as for visual stimuli involving reproducing designs from memory (Iverson, 1977). It is thought probable that the processes involved in these tasks, rather than the type of material to be remembered, is the factor, which leads to sexual dimorphism in memory abilities (Halpern, 1996). Some of these sex differences are relatively small, whereas others are moderate in size. The magnitude of sex differences in specific aspects of memory performance will be reviewed quantitatively in Chapter 3, using meta-analysis.

1.3. Theoretical explanations for sex differences

Across disciplines, theories have been proposed to explain sex differences in cognition. Whilst Self-Efficacy (Bandura, 1986), Cognitive Developmental (Kohlberg, 1966), Evolutionary (Silverman and Eals, 1992;

Eals and Silverman, 1994; Gaulin, 1995) and Psychoanalytic models have attempted to address this, the focus of this dissertation and research will be to outline hormonal and genetic theories for explaining such behaviours.

1.4. Biological Theories

The biological perspective focuses on the contribution that chromosomal makeup and gonadal hormones have to the observed sex differences in memory and cognitive abilities. This area of research also describes how hormones act to differentiate brain structure, organisation and function. Further, neurophysiological evidence has contributed to our understanding of how the gonadal hormones, particularly oestrogen, can influence memory and cognitive tasks that show sex differences. These biological systems overlap, e.g., genes and hormones operate on behaviour through neurological mechanisms and differences in sex hormones are dependent on genetically coded information.

1.4.1. Gonadal hormones and chromosomal makeup: Sexual differentiation of external and internal genitalia and other secondary sex characteristics.

The chromosomal sex of a child generally determines gonadal development. Females have two X chromosomes, whilst males have one X and one Y chromosome. Both males and females have gonads, which secrete hormones into the blood. Very early in gestation, these gonads are identical in males and females. However, information on the Y chromosome instructs the gonads to differentiate as testes. XX individuals do not have a Y chromosome and as a result of this, their gonads become ovaries (Wilson, George and Griffin, 1981). The two main classes of gonadal hormones are oestrogens and androgens. Testosterone is the predominant hormone produced by the testes and the most common androgen, whereas oestradiol is the predominant hormone produced by the ovaries and the most common oestrogen. There is also progesterone released from the ovaries.

At approximately eight weeks after fertilisation, males and females have two sets of reproductive ducts: A male *Wolffian* system, which has the potential to develop into the male reproductive ducts (e.g., the seminal

vesicles, which hold the fluid in which the sperm cells are ejaculated; and the vas deferens, through which the sperm cells travel to the seminal vesicles). They also have a female *Müllerian* system, which has the potential to develop into female ducts (e.g., the uterus; the upper part of the vagina; and the fallopian tubes, through which ova travel from the ovaries to the uterus, where they can be fertilised). In the third month of male foetal development, the testes secrete testosterone and *Müllerian-Inhibiting* substance. Testosterone stimulates the development of the Wolffian system, and the Müllerian-Inhibiting substance causes the Müllerian system to degenerate and the testes to descend into the scrotum (the sac that holds the testes outside the body cavity). The differentiation of the internal ducts of the female reproductive system is not under the control of ovarian hormones and so the ovaries are almost completely inactive during foetal development. The Müllerian system occurs in any foetus that is not exposed to testosterone during the critical foetal period (Wilson, George and Griffin, 1981).

Like the development of the internal reproductive ducts, the development of the external genitals is controlled by the presence or absence of testosterone. If testosterone is present at the appropriate stage of foetal development, male external genitals develop from the *bipotential*

precursor, however, if testosterone is not present, the development of the external genitals proceeds along female lines, from the same bipotential precursor. In sum, prenatally, males produce more androgen than females, leading to sexual differentiation in the direction of male-typical development of the internal and external genitalia and other aspects of physical appearance. In females, little androgen is produced, leading to female-typical development of these physical characteristics. Thus, sex differences in early physical development are due to the presence or absence of testosterone during critical prenatal and postnatal developmental phases and are referred to as *organising* effects.

Beginning with puberty, hormones have additional influences on physical development. In females, these influences include oestrogen-induced breast development and changes in the distribution of body fat that result in a more feminine body shape. In males, testosterone is responsible for the growth of facial, underarm and pubic hair. It also causes a deepening of the voice and muscle development, leading to a more masculine body shape. These physical developments are referred to as *activational* influences of hormones. Activational influences are described as temporary, occurring mainly during adult life, whereas organisational influences are more

permanent and occur mainly during critical periods of prenatal or neonatal development.

1.4.2. Activational and organisational influences of hormones on sexual behaviours in animals.

One approach to assess the effects of gonadal hormones on brain and behaviour has been the use of species other than humans. The extrapolation of findings from animals to humans has been questioned, as the effects of hormones on the behaviour of animals are generally assumed to be more dramatic than those observed in humans. This is due to the fact that in animals there are not the same social and cognitive factors intervening in the expression of behaviour, as there are with humans. Also, different findings can appear between species and breeds. Having stated these limitations, animal studies provide useful information that has generated hypotheses that can be tested in humans. Although a variety of animals have been studied to look at the effect of hormones on behaviour, rats have been used in main.

Researchers have used several methods to determine how hormones influence brain and behaviour. In male and female developing rats,

castration may be used to deprive the male rat of testosterone (secreted by the testes), whilst in female rats, ovariectomy (surgical removal of the ovaries) may be used to deprive the rat of hormones secreted by the ovaries. Gonadectomy is a term that describes this technique for either sex. Another opportunity to study the influence of hormones on behaviour has been through hormone fluctuations throughout the oestrous cycle.

Activational effects

Sexual behaviours in adult male and female rats are under the control of ovarian and testicular hormones. Female rats display 4-5 day cycles of gonadal hormone release. There is a gradual increase in the secretion of oestrogen by the developing follicle in the 2 days prior to ovulation, followed by a sudden surge in progesterone as the egg is released. These surges of oestrogen and progesterone initiate *oestrous*. Oestrous is a period of 12 to 18 hours during which the female is fertile, receptive (displaying the lordosis position when mounted) and proceptive (displaying behaviours to attract the male, such as hopping, darting and ear wiggling) (Beach, 1942; Boling and Blandau, 1939). Male rats do not have an oestrous cycle. They produce large amounts of androgens, including testosterone. These levels remain approximately constant and ensure maintenance of sexual interest and behaviour. In response to proceptive behaviours from the

female, the male mounts the female. After several mounts the male inserts his penis into the vagina and ejaculates. Ovarian hormones control female sexual behaviours and the testicular hormones regulate male sexual behaviours. Copulation is enabled by these mutual sexual behaviours (Beach, 1944; Davidson, 1969; Gorski, 1974).

Organisational effects

As previously mentioned, organisational influences of hormones are generally viewed as permanent and long lasting. As a consequence, when adult male and female rats are administered cross-sex hormones, a reversal of sexual behaviour is not observed. Administering ovarian hormones to adult male rats does not lead to lordosis. Similarly administering testicular hormones to adult female rats does not lead to mounting behaviours (Goy and McEwen, 1980). During critical periods of perinatal development, the brain has been hard-wired or organised to produce differential sexual behaviours that cannot be reversed. However, if females are treated with testosterone early on in life (day 1) and later treated with testosterone during adulthood, then male-typical sexual behaviours occur, such that high levels of mounting behaviours are displayed. Further, male rats deprived of testosterone at birth via castration will show reduced, if any, mounting behaviours (Goy and McEwen, 1980). Therefore, the development of

sexual behaviours in adult rats is dependent on both organisational and activational hormone environments.

Hormonal influences in other species

Whilst rats have been used in main to study the effects of gonadal hormones, similar findings have been confirmed in other species, including hamsters, mice, dogs, guinea pigs, sheep and rhesus monkeys (Hines, 1982). Differences among species typically involve the critical period of time that the hormones are influential to development. Further the particular hormones involved can differ from species to species.

1.4.3. Ovarian hormonal influence on sexual differentiation of sexual behaviour: Animal studies

Masculinising effects

The evidence presented so far has proposed that the presence of testicular androgens in early life leads to development of male sexual behaviours and the absence of androgen leads to the development of female sexual behaviours. A smaller area of research however has concentrated on the role that the ovarian hormones have in the development of sexual behaviours. As previously mentioned, with female development of physical

sexual characteristics, ovarian hormones have a minor, if any, role. However, some evidence has suggested that male-typical sexual behaviours occur in females when oestrogen is administered prenatally or neonatally to genetic females i.e., increased mounting and less lordosis (Collaer and Hines, 1995; Goy and McEwen, 1980). Therefore, it would appear that behavioural effects of exposure to oestrogen parallel those of exposure to testosterone.

These masculinising effects of oestrogen can be explained with the theory of aromatisation. Although testosterone is viewed in main as the fundamental vehicle of masculinisation, its actions often depend on its subsequent metabolism to substances, such as oestradiol or dihydrotestosterone (DHT). This conversion typically occurs outside the gonads, including in the tissues of the nervous system (MacLusky and Naftolin, 1981). The nervous system contains two critical enzymes. The first enzyme, *aromatase*, metabolises testosterone to oestradiol and the second enzyme, *5-alpha-reductase* (5- α R), converts testosterone to DHT. The oestradiol metabolised within the brain then acts through neural oestrogen receptors to produce masculine patterns of brain development and behaviour. Female rat brains do not get masculinised prenatally by the mothers' oestradiol, which circulates through the foetal blood supply, due

to alpha fetoprotein (AFP) present in the blood during the perinatal period. AFP deactivates circulating oestradiol by binding to it. However AFP does not bind to testosterone. Therefore, testosterone can travel from the testes to the brain, where it enters cells and can be converted to oestradiol. The oestradiol is not bound by AFP in the brain because AFP does not penetrate the blood-brain barrier (See Figure 1).

Figure 1: How oestradiol (an oestrogen) influences sexual differentiation: The process of aromatisation.

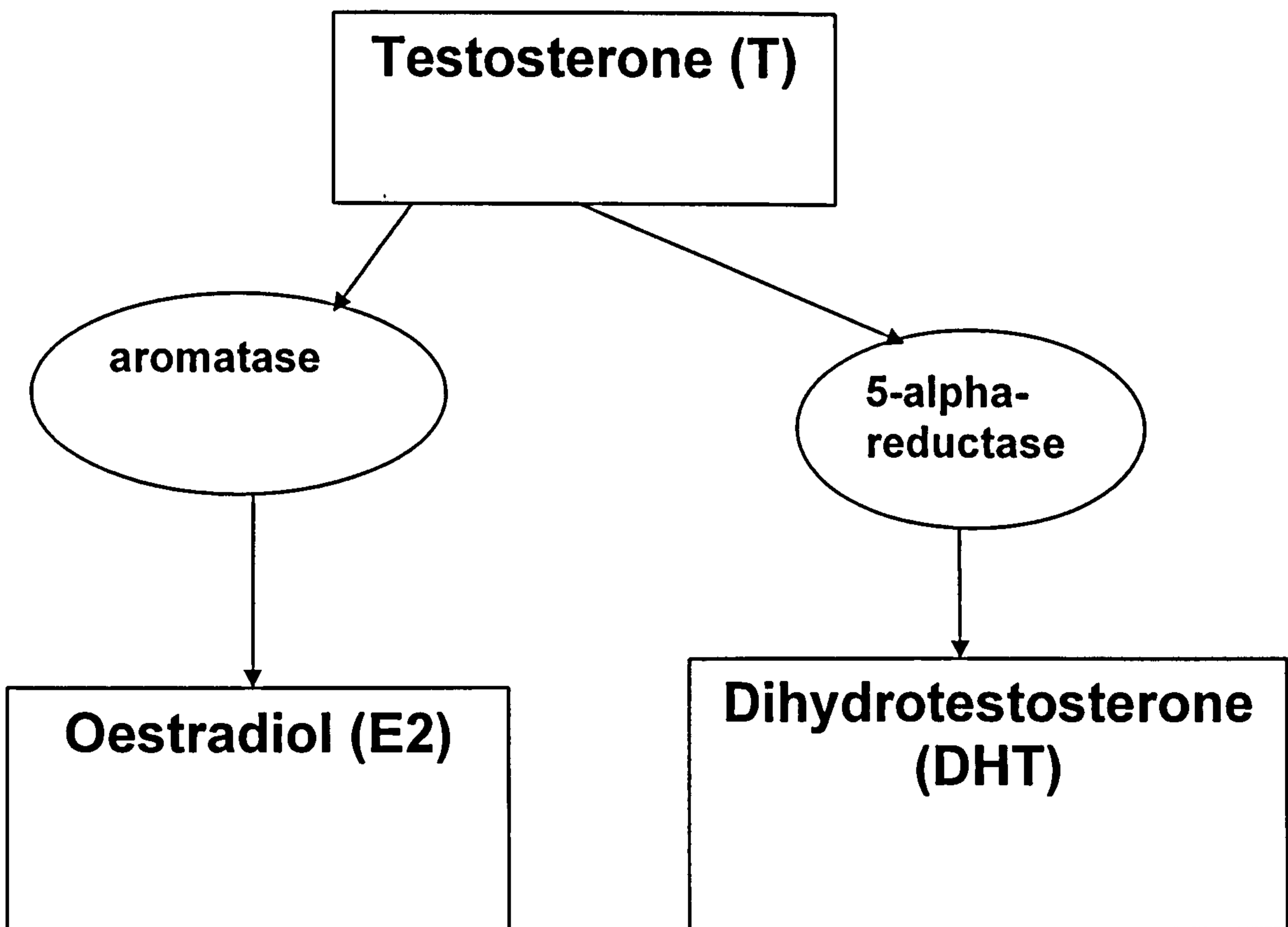


Figure 1. Testosterone (T) can be converted to oestradiol (E2) through the action of the enzyme aromatase before acting to produce neural and behavioural effects. Testosterone can also be converted to dihydrotestosterone (DHT) through the action of the enzyme 5-alpha-reductase before acting to virilise external genitalia in males. In rodents, and perhaps in primates, testosterone is converted to E2 within the brain before exerting many of its masculinising and defeminising effects. In contrast, although DHT may have some neurobehavioural effects, these appear to be far more limited than are the effects of E2 on the brain. DHT also is the primary cause of virilisation of the external genitalia, whereas E2 does not influence the external genitalia (For a review see Collaer and Hines, 1995; Hines, 2002).

Feminising effects

Whilst oestrogens can masculinise behaviour in females, other researchers have examined the feminising effects of ovarian hormones on sexual behaviour. When female rats are neonatally exposed to testosterone, female sexual behaviours such as lordosis are inhibited. However, such inhibition of these behaviours did not occur when the ovaries were retained. Higher response rates of lordosis were recorded (Blizard and Deneff, 1973). Similarly, when comparing postpubertally ovariectomised female rats with those ovariectomised neonatally, the former group displayed more lordosis as adults (Sodersten, 1976). This suggests that neonatal ovarian hormones play a feminising role in sexual differentiation. Other female rat sexual behaviours, such as hopping, darting and ear wiggling have been studied. Female rats that were ovariectomised postpubertally and oestrogen-primed showed higher proceptive behaviours compared to those that were ovariectomised neonatally (Gerall, Dunlap and Hendricks, 1973). All the above evidence can be interpreted to support that ovarian oestrogen may be necessary in organising receptive and proceptive behaviours. Further there is evidence to suggest feminising effects of ovarian hormones in male rats. Male rats that were gonadectomised neonatally and then administered ovarian implants or low-dose oestrogen treatment at puberty, displayed more receptive behaviours than male control rats that had only been

gonadectomised (Gerall, Dunlap and Hendricks, 1973). These reports suggest that oestrogen may be involved in feminising not only the female, but can have activational feminising effects on the male rat.

1.4.4. Testicular hormonal influence on sexual differentiation of the brain: Animal studies

Biological theorists propose that gonadal hormones guide brain development prenatally or neonatally and that this causes certain parts of the brain to develop in males and females in structurally different ways. This, alongside activational effects at puberty could contribute to the observed sex differences in behaviour (Collaer and Hines, 1995).

The corpus callosum

The corpus callosum (CC) is a collection of neural fibres that connects the two hemispheres in the brain and transfers information from one to the other. The CC in male rats is larger than that in female rats, and this size difference is uncorrelated with total brain weight (Zimmerberg and Mickus, 1990; Denenberg, Fitch, Schrott, Cowell, Denenberg and Waters, 1991).

Sexually dimorphic structures identified in the area of the CC may be altered by the administration of cross-sex hormones. Administering testosterone to newborn female rats leads to the development of a CC that is the size of that in males (Denenberg, Berrebi and Fitch, 1989; Fitch, Berrebi, Cowell, Schrott and Denenberg, 1990). However, this effect was only observed in handled female pups (Denenberg, Fitch, Schrott, Cowell and Waters, 1991). Handling is a procedure that involves removing the newborn pups from the cage in which they were born, leaving the mother in this cage. The pup is then placed in a can containing shavings. There the pup stays for 3 minutes, before returning the pup to its former cage (Denenberg, 1977). This procedure is repeated from day 1 to day 20. At day 21 there is weaning. The handling procedure has impacts on adrenal corticosteroids. Masculinisation of the CC occurs in females only when administered testosterone is combined with handling (Denenberg, Brumaghim, Haltmeyer and Zarrow, 1967). Furthermore, when an anti-androgen is given to pregnant rats, the CC in their male offspring is smaller (Fitch and Denenberg, 1998). Castration of handled male pups (day 1 of life) did not alter CC size in adulthood (Fitch et al, 1990; Denenberg et al, 1991) suggesting that during prenatal life, organising effects on the CC have already been established.

The hypothalamus

The hypothalamus is an area of the brain that influences reproductive behaviour and controls the release of reproductive hormones from the pituitary gland. In the 1970s, structural differences between the male and female hypothalamus were discovered in rats. Sex specific patterns of neuronal and dendritic development in the hypothalamus were identified (Raisman and Field, 1971). Further, a nucleus in the medial preoptic area of the rat hypothalamus was several times larger in males and this sex difference is thought to develop under the influence of early sex hormones. This nucleus was named the sexually dimorphic nucleus of the pre-optic area (SDN-POA) (Gorski, Gordon, Shryne, and Southam, 1978). Similar sex differences in this area of the brain have been found in other species such as ferrets, guinea pigs, gerbils and rhesus monkeys (Hines, Davis, Coquelin, Goy and Gorski, 1985; Byne, 1998; Commins and Yahr, 1984; Tobet, Zahniser and Baum, 1986).

At birth, the sexually dimorphic nuclei of male and female rats are the same size. In the first few days after birth, the male SDN-POA grows at a high rate and the female SDN-POA does not (McEwen, 1987). Castrating 1-day-old male rats significantly reduces the size of the SDN-POA as adults, and thus feminises this structure, whereas injecting neonatal

(newborn) female rats with testosterone significantly increases the size of the SDN-POA, and thus masculinises this structure (Gorski, 1980).

1.4.5. Ovarian hormone influence on sexual differentiation of the brain: Animal studies

The Corpus Callosum

Ovarian hormones also influence the CC. This was demonstrated when male and female pups (4 days old) were administered the oestrogen receptor blocker, tamoxifen. This resulted in an increase in callosal area in females, but not males (although marginally significant) (Fitch et al, 1990), suggesting oestrogen removal during development led to masculinisation. In support, further findings revealed that when neonatally handled females were ovariectomised on either day 8, 12 or 16, all three ovariectomised groups had significantly larger callosa in adulthood than control female littermates (Fitch et al, 1990). As callosal area did not differ between the three groups, this suggests that the sensitive periods for manipulating ovarian hormones exists to at least day 16. These results that oestrogen is necessary to feminise the female rat's corpus callosum have been confirmed elsewhere in both handled and non-handled females (Mack, Fitch, Cowell, Schrott and Denenberg, 1993). As previously mentioned,

testosterone effects on the female CC were only observed in conjunction to handling, whereas effects of ovariectomy on the female CC occurs irrespective of whether pups were handled or not. This may be due to the later sensitive period for manipulating ovarian hormones as opposed to testosterone manipulations.

As no relationship between callosal size and the oestrous cycle have been found (Mack, Fitch, Hyde, Seaman, Bimonte, Wei and Denenberg, 1996) and further as postpubertally ovariectomised females (at 78 days) showed no difference in CC size versus sham-operated female littermates (Mack, Fitch, Hyde, Seaman, Bimonte, Wei and Denenberg, 1996), it is probable that oestrogen effects on the CC are organisational rather than activational. It would also appear from the evidence discussed that exposure to testicular androgens is necessary during the perinatal period and females need exposure to ovarian hormones (although not necessarily oestrogen-specific) during a period that may extend beyond puberty for the CC to develop in a sexually dimorphic manner (Fitch and Denenberg, 1995).

The hypothalamus

As previously noted the SDN-POA is larger in adult male rats than adult female rats. Administering the oestrogen antagonist, tamoxifen, to female

rats decreases the size of the SDN-POA and so has been suggested to defeminise this structure (Dohler, Hancke, Srivastava, Hofman, Shryne and Gorski, 1984a; Dohler, Srivastava, Shryne, Jarzab, Sipos and Gorski, 1984b). Further research suggests that low levels of oestrogen are required for feminisation of this structure. When neonatal female rats were treated with oestrogen, the size of their SDN-POA was reduced in adulthood (McCarthy, Schlenker and Pfaff, 1993). Such evidence emphasises organisational influences of oestrogen in the development of this sexually dimorphic structure.

Other research acknowledges activational influences of oestrogen in hypothalamic structural development. Researchers looking at the hypothalamic anteroventral preoptic nucleus (AVPV) have found that it is significantly larger in female rats (Bloch and Gorski, 1988). Further, when male rats were castrated after puberty and then administered oestrogen and progesterone, the treatment feminised this structure, making it larger. These males also had a smaller SDN-POA when compared to control male rats and those rats gonadectomised only (Bloch and Gorski, 1988). These findings and later evidence that sex differences in the AVPV emerge at puberty (Davis, Elihu, Shryne and Gorski, 1993), suggest that oestrogen can have influences on hypothalamic structures later on in life.

Dendritic spine density of ventromedial hypothalamic neurons is reported to vary across the oestrous cycle in rats. Further, ovariectomy in female adult rats reduced density whereas treatment with either oestrogen or oestrogen with progesterone increased density (Frankfurt, Gould, Woolley and McEwen, 1990).

Altogether, the research outlined suggests above that activational influences of oestrogen can also involve structural changes in the hypothalamus. This contradicts the traditional view that structural changes are permanent and restricted to the early organisational period. Further, whereas testosterone seems to be more influential in organising these structural changes, oestrogenic influence on particular sexually dimorphic brain structures can be both organisational and activational.

1.4.6. Influence of hormones on non-reproductive behaviours in animals.

Gonadal hormones affect a number of non-reproductive behaviours in rats. These include exploratory behaviour, aggression, play, taste preference, feeding, active avoidance learning and maze learning (Collaer and Hines, 1995; Goy and McEwen, 1980; Hines and Gorski, 1985). It is important to

highlight here that all these behaviours show sex differences, therefore it would appear that hormones appear to specifically influence characteristics that show sex differences.

The present thesis focuses on hormonal influences on memory and cognition, therefore the subsequent sections will focus on this.

It has been hypothesised that sex-related differences in memory and cognition are due, in part, to organising hormonal influences during early development, in conjunction with activating effects of hormones following puberty (Goy and McEwen, 1980; Collaer and Hines, 1995). Findings of oestrogen receptors located in brain regions, including the hippocampus, also suggest a possible hormonal significance in cognitive functions involving learning and memory (Eichenbaum and Otto, 1992; Loy, Gerlach and McEwen, 1988; O'Keefe and Handa, 1990). For instance, the hippocampus has been referred to as a 'cognitive map' because of its function in mapping spatial relations (O'Keefe and Nadel, 1978).

1.5. Evidence for gonadal hormone influence on memory and cognitive abilities: Animal studies

As with research into sexual differentiation of brain and sexual behaviour, one approach to assess the effects of gonadal hormones on memory and cognition has been the use of other species. Studies of rats have established that oestrogen can influence performance on learning and memory tasks. Abilities including spatial working memory and reference memory can be assessed in rats. For obvious reasons verbal abilities cannot be assessed.

Organisational effects

Studies have demonstrated organisational effects of hormones on spatial memory in rats, where hormone exposure is manipulated perinatally. Research has shown male rats to outperform female rats on visual-spatial maze tasks (Dawson, Cheung and Lau, 1975; Gaulin and Fitzgerald, 1986; Williams, Barnett and Meck, 1990; Bimonte and Denenberg, 2000). Furthermore, neonatal castration of male rats feminises (and thus reduces) spatial performance, whereas testosterone administered to neonatal female rats masculinises (and thus improves) performance on spatial tasks (Dawson, Cheung and Lau, 1975; Roof and Havens, 1992). Subsequent research has looked at female rats that were administered oestrogen

subcutaneously via injection prior to puberty, 1-9 days after birth. When compared with untreated female controls, performance in a 12 arm radial maze, on which males generally perform better than females, was facilitated in only those administered oestrogen, whereas neonatally castrated male rats had impaired performance on this radial maze task (Williams, Barnett and Meck, 1990). This suggests that early exposure to oestrogen improves the performance of female rats on this task. It has been reported that male rats make fewer errors than female rats on both 8 and 12 arm versions of this task (Beatty, 1984; Mishima, Higashitani, Teraoka and Yoshioka, 1986). As with findings discussed in previous sections, of oestrogen masculinising sexual behaviours in female rats, it has been proposed that these masculinising effects of oestradiol may be dependent on the aromatisation of testosterone to oestrogen, which plays a key role in the facilitation of male sexual behaviour (Williams and Meck, 1991).

Activational effects

Activational effects have been studied in adult rats that undergo hormone replacement following gonadectomy or by correlating behavioural changes with fluctuations in hormone levels over their oestrous cycle. When adult male and female rats were gonadectomised and high dose oestradiol (a dose that generated pro-oestrous levels) administered subcutaneously to some of

the rats, there was a marked reduction in the number of spatial working memory errors in an 8-arm radial maze in those treated with oestrogen. This was observed after delayed periods of between one and five hours. However, this oestrogenic effect was evident in the male rats only (Luine and Rodriguez, 1994; Luine, 1997). Further when adult female rats were ovariectomised at 35 days and then administered low dose oestradiol (a dose that generated di-oestrous levels), these rats outperformed their untreated controls on an 8-arm radial maze (Daniel, Fader, Spencer and Dohanich, 1997). Whilst this may suggest any oestrogenic influence on spatial working memory in female rats is dose-dependent, when both high and low doses of oestradiol were delivered by the same method to adult female rats that had just been ovariectomised, a reduction in the number of spatial working memory errors committed during an acquisition task was observed. These studies demonstrated an improved arm choice accuracy in a more cognitively demanding, 12-arm radial maze with baited arms. However, after 12 months of oestradiol replacement, this improvement was not evident, suggesting short-term, but not long-term oestradiol replacement enhances working memory in adult female rats (Williams, Raines and Meck, 1994; Williams, 1996).

To ascertain whether the type of memory processing is specific to oestrogenic influence, the 8-arm radial maze was modified to assess both working and reference memory performance. Female rats were ovariectomised at 35 days and then administered low dose oestradiol. These treated rats outperformed their untreated controls on the working, but not reference, memory components of the task (Fader, Johnson and Dohanich, 1999). These findings may suggest that tasks requiring working memory are exclusively sensitive to oestrogen enhancement.

Other measures of learning and memory have also been used when investigating the effects of oestrogen on performance in rats, including the Morris water maze, a spatial reference memory task. Results from studies with a variety of species of rodents have revealed that gonadally intact adult males generally acquire the water maze task faster than gonadally intact adult females (Perrot-Sinal, Kostenuik, Ossenkopp and Kavaliers, 1996; Galea, Kavaliers and Ossenkopp, 1996; Galea, Kavaliers, Ossenkopp, Innes and Hargreaves, 1994; Williams and Meck, 1991). When a water-soluble form of oestradiol was given to gonadectomised adult females and gonadally intact adult male rats, within an hour after a training session performance on a retention trial was enhanced (Packard, Kohlmaier and Alexander, 1996; Packard and Teather, 1997; Sandstrom and Williams,

2001). This suggests that oestrogen helps to consolidate memory, that oestrogen effects are not task specific and contradicts previous ideas that oestrogenic influence is exclusive to spatial working memory aspects of a task.

Recent research has hypothesised that oestrogen influences the strategies used to solve the task. Young adult female rats were ovariectomised for 21 days and trained after short-term (acute) hormone or placebo treatment. The dose of oestrogen produced circulating oestradiol levels that were higher than those found at pro-oestrous. The training involved learning *place* and *response* tasks. The place task involved training the rats to find food in the goal arm located in a fixed position relative to the extramaze room cues. The remaining arm locations were assigned randomly as start arms and counterbalanced across the training trials. When the rat found the food, place learning was said to have occurred. For the response task, rats were trained to make either a left or a right turn to find food in the goal arm. The goal arm was varied across training but maintained its position relative to the start arm with respect to the correct turn. Rats given oestradiol before training learned the place task faster than those without. Conversely, rats not given oestradiol performed better on the response task and outperformed the rats given oestradiol (Korol and Kolo, 2002).

The finding of an oestrogenic influence on place learning, but not response learning, may relate to previous findings outlined on the radial arm maze tasks. It has been suggested that in the radial arm maze, there may be a conflict between hippocampal and non-hippocampal dependent strategies e.g., place/working memory versus response/reference memory strategies, both offering reasonable solutions to the task. As oestrogen effects may be bias towards the use of hippocampal-dependent strategies, improved acquisition of the radial arm maze may be due to oestrogenic influences on working memory functions (Korol and Kolo, 2002).

There also are some reports suggesting that high levels of either endogenous oestrogen (secreted by the ovaries) or exogenous oestrogen (administered) correlate with lower maze acquisition and retention in female rats (Frye, 1995; Galea, Kavaliers, Ossenkopp and Hampson, 1995; Korol, Unick, Goosens, Crane, Gold and Foster, 1994; Warren and Juraska, 1997). Furthermore some studies have found no influence of oestrogen on memory in rats (Stackman, Blasberg, Langan, and Clark, 1997; Berry, McMahan and Gallagher, 1997).

It has been suggested that these inconsistencies among studies may be due to several factors other than hormones, such as: the different tasks used between studies to assess hormonal action on cognition; sex and strain of rat; manner of hormone manipulation and reproductive history (Korol and Kolo, 2002). In reviewing these studies, there seems to be no consensus of the exact nature of the effects of oestrogen on spatial memory tasks in female rats. It is likely that a complex interaction of these factors, yet to be identified, would explain the nature of oestrogenic influence on spatial memory and learning in rats. The dichotomies studied (low dose versus high dose / reference memory versus working memory) fail to account for the complexities of oestrogen's actions. The theory that oestrogen affects the strategy used to solve spatial memory tests in rats provides an interesting, yet incomplete explanation for the mixed findings of enhancement and impairment on a variety of cognitive tasks. Further research may clarify specific hormone effects on memory performance. However, the consistent finding from these studies is that oestrogen acts quite specifically on cognitive tasks that are sexually dimorphic in rats.

Rhesus monkeys

Activational influences of oestrogen on cognitive performance have also been studied in female rhesus monkeys. In one study, four young (5-7 year

old) female rhesus monkeys were daily tested on matching to sample tasks (immediate and delayed recall) and a spatial delayed recognition span test (DRST) during the menstrual cycle. Performance on the hippocampal-dependent, DRST was significantly better during the follicular and luteal phases (when oestrogen levels are low) than during the peri-ovulatory phase (when oestrogen levels are at their highest) (Lacreuse, Verrault, James and Herndon, 2001). This supports research previously outlined that higher spatial memory performance is associated with lower levels rather than higher levels during the oestrous cycle in rats (Frye, 1995; Galea et al, 1995; Korol et al, 1994; Warren and Jurashka, 1997).

Cognitive decline, as measured by a delayed response test in female monkeys has also been associated with oestrogen deficiency in the menopause. The delayed response task involves the prefrontal cortex and other memory related structures in the medial temporal lobe (Roberts, Gilardi, Lashley and Rapp, 1997). Further evidence has examined the effects of ERT on cognition in female rhesus monkeys. Five aged female rhesus monkeys (21-24 year old) were ovariectomised long-term (10-16 years) and then administered oestrogen. They were then tested five days a week for nine months. The findings showed that oestrogen treated monkeys performed better than the placebo controls on the spatial DRST, however

this enhancement was limited to the working memory aspect of the task (novel sequences) and not the reference memory aspect of the task (repeated sequences) (Lacreuse, Wilson and Herndon, 2003). Findings parallel research previously outlined with rodents that demonstrated oestrogenic influence on working memory, but not reference memory (Fader, Johnson and Dohanich, 1999). Findings suggest it may be the type of memory processing involved in these tasks (working versus reference) that is important when considering oestrogenic influences on spatial memory in rhesus monkeys. Further research into oestrogenic effects on place and response learning in rhesus monkeys, would be informative here, to determine if oestrogen may also bias the strategies used to solve the task. Further the DRST shows a sex difference favouring males (Lacreuse, Herndon, Killiany, and Rosene and Moss, 1999), therefore findings may parallel those in female rats, that oestrogen is specifically sensitive to tasks that show sex differences in the rhesus monkey. However, until more research is carried with rhesus monkeys, using a variety of other measures that do and do not show sex differences, it is tentative to draw this conclusion.

1.6. More evidence for gonadal hormone influences on cognitive abilities II: Human studies

The androgen/oestrogen balance model proposes an optimal balance of androgens and oestrogens in the expression of male-typical cognitive behaviours in humans (Nyborg 1984; 1988; 1990). A curvilinear relationship was predicted between oestradiol and spatial abilities. Females have more oestradiol than males, which exceeds the optimal level, and this is used to explain the superior performance of spatial abilities in males. Nyborg proposes that prenatal hormones determine the sensitivity to hormones secreted at puberty for each individual and so stresses the importance of both activational and organisational hormonal influences in determining spatial ability.

Nyborg developed this 'optimal oestradiol range' theory from some of his own observations. He studied a group of women with Turner Syndrome, a genetic abnormality that results in reduced amounts of sex hormone available during development. Subsequently women with Turner Syndrome have plasma oestradiol levels that are abnormally low. These individuals performed poorly in mathematics and spatial ability, however short-term (average of 1 year) oestradiol treatment results in improved spatial

performance, to a level comparable to their age-matched sisters. Conversely, when long-term oestradiol treatment (average of 8 years) was given to these women, lower than average female spatial ability was observed (Nyborg and Nielsen, 1981). The authors hypothesise that short-term oestradiol treatment raises their oestrogen to below the optimal level for the expression of spatial abilities, the normal female level. Long-term oestradiol treatment may infringe the optimal oestradiol range. Therefore, this might explain the impairment of spatial ability. Other research outlining cognitive ability in those with Turner Syndrome will be discussed later in section 1.6.1. Prenatal sex hormone abnormalities in humans.

Nyborg (1977) also drew upon his observations of pre- and post- pubertal males and females to support his theory of optimal oestrogen. He noted that spatial abilities in females (as measured by the Embedded Figures test, the Rod and Frame test, and Money's Road-Map test) declined after puberty, however, no decline in these abilities was observed in post-pubertal males. To explain these findings, Nyborg puts forward that the rise in oestradiol and testosterone in boys during puberty is assumed to leave their spatial abilities unaffected, at a level around the optimal range, whereas the rise in oestradiol in girls during puberty exceeds the optimal range and has a subsequent deteriorating influence on spatial ability.

Petersen (1976) studied whether physical manifestations of sex hormone influence cognitive functioning in male and female adolescents at ages 13, 16 and 18. Sex hormone influence was inferred from the degree of secondary sex characteristic development as it has been proposed that a relative abundance of oestradiol favours feminine secondary sex characteristics (Marshall and Tanner, 1969), whereas abundance of testosterone leads to masculine secondary sex characteristics (Marshall and Tanner, 1970). Physical measures of femininity and masculinity were ratings of whole nude body photographs of participants. Less physically feminine (androgynous) females showed higher scores on the Block Design test (test of spatial ability), whereas more physically masculine males showed lower scores on this task, than less physically masculine females. This evidence seems to support Nyborg's optimal balance of hormones theory, however, the assumption that more physically masculine males have different levels of sex hormones than less physically masculine males and less physically feminine females, could not be verified in relation to hormonal impact on spatial ability, as actual hormone levels were not measured.

Whereas Petersen emphasises the importance of androgen in the expression of spatial abilities, Nyborg emphasises the importance of oestrogen. However, it is still unclear whether it is androgen or oestrogen that is the important hormone, as previously mentioned, testosterone can be converted to oestradiol.

1.6.1. Prenatal sex hormone abnormalities in humans.

Research into the relationship between early levels of gonadal hormones and cognitive abilities, has studied individuals who were exposed to abnormal hormone environments pre or neo-natally, either because of genetic disorders or because their mothers were prescribed hormones during pregnancy. Whilst we must be cautious in generalising these findings to make inferences to normals, these people provide information on how sex hormones may or may not influence behaviour in humans.

Between the 1940s and 1970s, synthetic oestrogens were prescribed to pregnant women. The aim was to reduce rates of miscarriage (Noller and Fish, 1974). The practice of giving the hormone, diethylstilbestrol (DES) was withdrawn due to the increase found in vaginal and cervical cancers in female offspring of these women (Herbst, Ulfelder and Poskanzer, 1971).

In 1962, the Food and Drug Administration (FDA) of the US Department of Health and Human Services also declared DES was not found to be effective in preventing miscarriage.

Research looking at those who have been exposed prenatally to DES has found that their IQ is no different to their sibling controls (Reinisch and Karow, 1977). Further when the daughters who were exposed prenatally to DES were studied later in life, their verbal and visual-spatial abilities were no different to unexposed sisters (Hines and Shipley, 1984). Although the tests used by Hines and Shipley (1984) did not show large sex differences, a second study found similar results, this time using a wider range of tests, including the measure of 3-D Mental Rotations that shows the largest sex difference (Hines and Sandberg, 1996). Additional evidence comes from a larger scale, double-blind, placebo-controlled study, which showed no difference between DES-exposed and unexposed girls and boys in scores on subscales of a college entrance examination, despite seeing significant sex differences on the subscales. The authors however did find one difference between the DES-exposed men and placebo treated men. DES exposed men scored higher on the Social Science subtest (a test which shows a sex difference favouring males). The authors' interpretation was

that this finding was due to chance rather than possible masculinising effects of prenatal oestrogen exposure (Wilcox, Maxey and Herbst, 1992).

Other research has found that males exposed to DES prenatally had been feminised. 16-year-old boys who had been exposed prenatally to oestrogen and progesterone had been feminised, based on their impaired performance on the Embedded Figures test (a task that favours males), compared to matched controls (Yalom, Green and Fisk, 1973). However, the Embedded Figures test actually shows small sex differences, if any, and this impairment was not later replicated (Kester, Green, Finch, Williams, 1980). Another study compared ten males exposed to DES with their matched, sibling control brothers. Lower performance in spatial ability (measured by Picture Completion and Block Design, from the Wechsler intelligence scales) was seen in those exposed to DES (Reinisch and Sanders, 1992). Therefore there is inconsistent evidence to suggest that early exposure of oestrogen in humans influence cognitive development.

Complete Androgen Insensitivity Syndrome (CAIS) is a disorder in which a genetic male is not responsive to male sex hormones. This leads to the development of female external genitalia. As a psychological and practical solution, female socialisation is advised. One study found that these

individuals have IQs in the normal range, although their verbal scores were higher than their performance-perceptual scores, which were also lower than male and female controls. Deficits were also observed in visual-spatial skills (Imperato-McGinley, Pichardo, Gautier, Voyer and Bryden, 1991). It is difficult to draw conclusions that such cognitive deficits are due to androgen insensitivity, as the tests employed in this research do not show substantial sex differences. Rather they rely on ability to respond rapidly under timed conditions.

Studies of females with Turner Syndrome have also contributed knowledge into the effects of hormones on cognitive abilities. This disorder is characterised by a genetic abnormality of a missing, second sex chromosome; i.e., 45XO – forty-five chromosomes and only a single X sex chromosome - leading to underdeveloped ovaries and low levels of hormones (Jones, 1989). In other cases part of the X chromosome is lost or there is a combination of normal and abnormal cell lines, known as mosaicism (Ross, 1990). Consequently, females with this condition have very low levels of both male and female hormones. Whilst these females' IQ remain in the normal range for verbal IQ (Garron, 1977), selective impairments occur in a variety of cognitive tasks that show sex differences, assessing visual-spatial ability (Hines, 1982), Verbal Fluency and some

aspects of visual memory (Murphy, Allen, Haxby, Largay, Daly, White, Powell, Schapiro, 1994). Impairments are also shown on tasks of attention (Rovet, 1993), calculating ability (Temple and Marriott, 1998) and more so on tasks that show sex differences rather than on tasks that do not (Collaer, Geffner, Kaufman, Buckingham and Hines, 2002). Hormone replacement therapy does not have an impact on most of the cognitive deficits of Turner Syndrome (Ross, Stefanos, Kushner, Zinn, Bondy and Roeltgen, 2002) and it is suggested that factors other than hormones may contribute to these deficits e.g., genes, height and sometimes general health (Collaer and Hines, 1995). A recent study examined a variety of spatial skills, including Mental Rotation, the Rod and Frame task and the Paper Folding task in females with Turner Syndrome (n=9). These females were being treated with oestrogen for delayed puberty. The purpose of this study was to ascertain whether this hormone treatment that stimulated early, middle and late puberty influenced these spatial abilities. No activating effect of oestrogen was seen on these spatial measures. These findings suggest that spatial behaviour is not influenced by actively circulating hormones that occur during early, middle or late puberty (Liben, Susman, Finkelstein, Chinchilli, Kunselman, Schwab, Dubas, Demers, Lookingbill, D’Arcangelo, Krogh and Kulin, 2002).

Another disorder involving hormonal abnormality during early development is Congenital Adrenal Hyperplasia (CAH). CAH is an autosomal recessive disorder causing an enzymatic deficiency, usually in the enzyme 21-hydroxylase, which prevents release of the hormone cortisol from the adrenal cortex. This results in compensatory adrenal hyperactivity and the excessive release of adrenal androgens (New, 1998). Research assessing the impact of high levels of androgens on cognitive abilities suggests no difference between CAH females and controls on global IQ, however the pattern of findings describing their spatial and verbal abilities has been inconsistent. Some studies have found that females with CAH scored higher on spatial abilities than their unaffected sibling controls, suggesting that females with CAH may develop a more masculine cognitive style in spatial ability due to increased androgen exposure prenatally (Resnick, Berenbaum, Gottesman and Bouchard, 1986; Hampson, Rovet and Altmann, 1998). Others have reported no difference between those with CAH and their controls in terms of spatial ability (Baker and Ehrhardt, 1974; McGuire, Ryan and Omenn, 1975; Hines, Fane, Pasterski, Mathews, Conway and Brooks, 2003), whereas one study has reported a deficiency in spatial perception, alongside verbal deficits, in females with CAH (Helleday, Bartfai, Rizen and Forsman, 1994).

These discrepant findings might be due to the small samples in these studies and the different tasks used between studies with those showing larger sex differences being more sensitive to prenatal hormone exposure. To resolve these methodological issues, a recent large-scale study comparing CAH males and females with their sibling controls used two spatial tasks that show large and reliable sex differences. Females with CAH outperformed their sibling controls in targeting abilities, but did not perform any differently on Mental Rotations. Conversely, CAH males showed impairment on Mental Rotations but no difference on targeting abilities compared to their sibling controls. It is suggested that these findings could be explained by possible different critical periods for hormonal influences on targeting versus Mental Rotation abilities between males and females with CAH (Hines, Fane, Pasterski, Mathews, Conway and Brook, 2003).

Findings from those with CAIS, Turner Syndrome, CAH and those exposed to DES prenatally, provide insight into how prenatal hormones could influence some cognitive behaviours that show sex differences, but findings are weak and inconclusive.

1.6.2. Memory and cognition in postmenopausal women

The menopause occurs in women at approximately fifty years of age and is characterised by reduced ovarian activity and infertility. Oestrogen levels drop to approximately 16% of the levels found during fertility (Gow, Turner, and Glasier, 1994). During this stage, women may experience hot flushes, depression, anxiety, insomnia, vaginal dryness, decreased concentration and memory loss (Friedman, 1991; Lalumiere, Lorrain and Caron, 1991; Regestein, 1991). Hormone Replacement Therapy (HRT) in varying forms can be given to reduce some of these discomforts (Campbell and Whitehead, 1977). Preparations may be oestrogen based only, commonly referred to as Oestrogen Replacement Therapy (ERT); combination preparations of oestrogen with progesterone (EP); oestrogen with androgen (EA); progesterone only (P); or androgen only (A). HRT is also suggested to have a protective effect on deaths resulting from coronary heart disease and to reduce the risk of osteoporosis (Palacios, 1999).

Whilst there are reports of an increase in breast cancer associated with the use of HRT (Beral, Banks, Reeves, and Appleby, 1999), on balance, until recently it was thought that the benefits of HRT far outweigh the risks (Schneider and Jackisch, 1998). Opinion about the efficacy of HRT as a

safe treatment has altered in the last couple of years. In 1991, the National Institutes of Health began the first and only large study comparing the effects of HRT with placebos in healthy women. In July 2002, when researchers concluded that the drugs, oestrogen and progestin found in hormone replacement therapy had risks that clearly outweighed the benefits, the study was halted. The study was supposed to last until 2005, but was abruptly stopped when instances of heart attack, stroke, and breast cancer risk were associated with hormone replacement therapy. The 16,000 women participating in the hormone replacement therapy study were immediately sent letters instructing them to discontinue the use of the oestrogen-progestin combination drug 'Prempro'.

Prior to these recent cautions, studies of HRT were thought to provide a safe paradigm in which to monitor the activational effects of oestrogen on memory and cognition. Another situation in which an opportunity arises to study activational, hormonal influence on memory and cognition occurs in women who have been oophorectomised – had their ovaries surgically removed.

Research on postmenopausal women undergoing ERT provides support for an influence of oestrogen on memory and cognition. Improvements have

been reported on a verbal learning task, PAL, in postmenopausal women after 6 months of oestrogen treatment compared to untreated controls (Caldwell and Watson, 1952). This has been recently supported in a randomised, double-blind, placebo-controlled trial of postmenopausal women. Those receiving oestrogen showed better oral reading and verbal memory (assessed using the Wechsler verbal memory tests, Logical Memory and PAL), than the placebo group (Shaywitz, Naftolin, Zeltermann, Marchione, Holahan, Palter and Shaywitz, 2003). Additional evidence suggests that oestrogen administered to surgically postmenopausal women may help maintain or improve specific aspects of verbal memory with no influence on visual memory (Phillips and Sherwin 1992b; Sherwin, 1996; Carlson and Sherwin, 1998).

Other studies found that many aspects of cognitive performance improved in postmenopausal women on oestrogen. Oestrogen users have also been shown to perform better than non-oestrogen users on figural memory, a short-term visual memory task. Resnick, Metter and Zonderman (1997), found that ERT seems to protect against age changes in the Benton Visual Reproduction Test – BVRT (a measure of short-term visual memory, visual perception and constructional skills). Other authors concluded that HRT had an improving effect on cognitive functions in general, rather than a

specific effect on verbal memory (Hogervorst, Boshuisen, Riedel, Willeken and Jolles, 1999; Duka, Tasker and McGowan, 2000; Kimura, 1995). Furthermore, women subjected to hysterectomy or oophorectomy showed a significant decline in Mini Mental State Examination (MMSE), WMS subtests (Digit Span, visual memory, Logical Memory and mental control) at 3 and 6 months postoperatively, compared to the control group (Farrag, Khedr, Abdel-Aleem and Rageh, 2002). However, oestrogenic effects on memory following menopause are not always found (Ditkoff, Cracy, Cristo and Lobo, 1991; Barrett-Connor and Kritz-Silverstein, 1993; Binder, Schechtman, Birge, Williams and Kohrt, 2001).

It is thought that the inconsistencies among findings may be due to differences in hormone preparations, differing procedures and the use of different neuropsychological tests (Haskell, Richardson and Horwitz, 1997). In using neuropsychological tests to explore treatment effects it is important that the tests are piloted to ensure that ceiling or floor effects are not present. One study illustrates that oestrogen may be exerting an influence on brain activation, measured using Magnetic Resonance Imaging (MRI) techniques, however the test used may be too simple, resulting in ceiling effects on behavioural outcome measures. This study investigated brain activation patterns in postmenopausal women as they

performed verbal and non-verbal working memory tasks. Although ERT did not produce significant changes in performance, oestrogen increased activation in the inferior parietal lobule during verbal memory tasks and decreased activation in this area during storage of non-verbal tasks (Shaywitz, Shaywitz, Pugh, Fulbright, Skudlarski, Mencl, Constable, Naftolin, Palter, Marchione, Katz, Shankweiler, Fletcher, Lacadie, Keltz and Gore, 1999). The authors suggest that the failure to detect a change in performance coinciding with changes in brain activation may result from ceiling effects (Shaywitz et al, 1999).

Another reason for inconsistencies in the literature may be due to individual differences between participants. A recent meta-analysis of HRT usage for the prevention of cognitive decline showed that in symptomatic women (e.g., those who experience hot flushes, depression, anxiety, insomnia, vaginal dryness, decreased concentration and memory loss), postmenopausal ERT improved cognitive performance, especially in tests of verbal memory, vigilance, reasoning and motor speed. There were not consistent effects on visual recall, working memory, complex attention, mental tracking, or verbal function. It was suggested that symptomatic women taking oestrogen might perform better on cognitive testing because they have fewer hot flushes and sleep better or have improved mood.

Oestrogen does not seem to enhance cognitive function or mood in asymptomatic women (LeBlanc, Janowsky, Chan and Nelson, 2001).

Finally, it is suggested that different hormone preparations given to postmenopausal women might explain the differential findings among studies. Adding progesterone to oestrogen is suggested to have unfavourable effects on cognition. Increased risk of dementia and a deteriorating influence global cognitive functioning (as measured by the MMSE) has been reported in data collected from a large scale study investigating HRT and cognitive functioning in postmenopausal women (Rapp, Espeland, Shumaker, Henderson, Brunner, Manson, Gass, Stefanick, Lane, Hays, Johnson, Coker, Dailey and Bowen, 2003; Shumaker, Legault, Rapp, Thal, Wallace, Ockene, Hendrix, Jones, Assaf, Jackson, Kotchen, Wassertheil-Smoller and Wactawski-Wende, 2003). See Table 1 for a summary of past research involving HRT and cognition in women.

1.6.3. Memory and cognition throughout the menstrual cycle.

Levels of oestrogen and progesterone vary during the menstrual cycle in a cyclical fashion. During the premenstrual, menstrual and immediately

postmenstrual phases of the cycle, oestrogen and progesterone levels are low. At midcycle oestrogen, but not progesterone, peaks and then declines again to premenstrual levels

Past research assumes that this cyclical variation in gonadal hormones during the menstrual cycle leads to a concurrent variation in memory and cognitive abilities. It has been suggested that in the midluteal phase, when oestrogen levels are high, there is an enhancement of verbal abilities along with a depression of visual-spatial abilities, while the reverse occurs at menses, when oestrogen levels are low (Hampson and Kimura, 1988; Hampson, 1990a, b, c; Phillips, 1996). Maki, Rich and Rosenbaum (2002) found that there was a decrease in performance on Mental Rotations and improved perceptual motor skills and Verbal Fluency in the midluteal phase. Oestradiol, but not progesterone, levels correlated positively with Verbal Fluency and negatively with Mental Rotations, suggesting that oestrogen and not progesterone was responsible for the observed changes in cognition. However, similar associations of verbal and visual-spatial performance with cycle phase have not always been found (Black and Koulis-Chitwood, 1990; Gordon and Lee, 1993; Gaulin, Silverman, Phillips and Reiber, 1997; for a review see Epting and Overman, 1998). In regard to memory, Phillips and Sherwin (1992a) report significantly lower

visual memory in delayed recall during the menstrual phase compared to the luteal phase, but no differences between phases for other memory tests, such as Digit Span and PAL. See Table 2 for a summary of past research involving cognition and the menstrual cycle.

1.6.4. Hormones and cognition in men

Fewer studies have examined whether hormone levels influence memory and cognition in men than in women. However, it has been reported that spatial ability is better in men with low levels of testosterone than in men with higher levels (Gouchie and Kimura, 1991; Shute, Pellegrino, Hubert and Reynolds, 1983). These findings seem to conform to the proposal that, for males, high levels of androgens are associated with low spatial abilities (Petersen, 1976; Nyborg, 1984). Conversely, another study reports that androgens correlate positively with tests of spatial ability and negatively with tests of verbal ability in healthy young men (Christiansen and Knussman, 1987). More recently, a positive association was found between testosterone levels and performance on the MMSE, the Digit Symbol test (a perceptual motor task) and Trails (a spatial task), suggesting that testosterone has a general positive influence on cognitive functioning in older men (Yaffe, Lui, Zmuda and Cauley, 2002).

Other research suggests there is an association between oestrogen, not testosterone, and visual memory in males. Kampen and Sherwin (1996) studied cognitive performance in healthy middle-aged men. Two tests of visual memory were used - the BVRT and Visual Reproduction (VR) from the Wechsler Memory Scale (WMS). Attention and visual-spatial ability were also assessed. Those with higher levels of oestradiol performed significantly better than those with lower levels on both measures of visual memory. However, testosterone or oestradiol did not relate to scores on any of the other memory or cognitive measures: Visual PAL (WMS), Verbal PAL (WMS), Figural memory (WMS), paragraph recall (WMS), Mental Rotations, Digit Span (WMS) and a block span test.

Research has investigated the effects of testosterone treatment on cognition in men. In older men, an enhancement in visual-spatial ability was observed following Testosterone Replacement Therapy (TRT) to raise levels comparable to those in younger men (Janowsky, Oviatt and Orwoll, 1994). A review of the effects of androgen therapy in aging men concluded that the potential uses of these replacements are still speculative (Morrison, 1997). It is suggested that the relationship between testosterone levels in men and women and cognitive function is a complex one that is influenced by multiple hormonal and non-hormonal variables (Morrison, 1997).

It is difficult to ascertain whether oestrogen or testosterone is important in the expression of spatial ability in men, because as previously mentioned testosterone can be converted to oestradiol. Like other areas of research on hormones and human cognition, studies relating oestradiol or testosterone to cognitive performance have produced inconsistent results.

1.6.5. The effects of time of day and year on memory and cognition

As previously outlined, memory and cognition has been suggested to vary with monthly hormone fluctuations in women. Further research has looked into whether sex differences in cognitive function vary with the time of day. Testosterone levels are higher in both males and females early in the morning compared to later in the day (Dabbs, 1990). Further it has been reported that spatial ability improves in men from early to late morning whereas spatial ability declines from early to late morning in women (Moffat and Hampson, 1996). A different pattern was reported later when comparing morning and afternoon performance on a spatial task, Mental Rotations. Both males and females improved on this task. Further, both males and females improved later on in the day, on a task favouring females, the Purdue peg board (Sanders, Sjodin and de Chastelaine, 2002). Both studies suggest that for both sexes there may be cognitive changes

that accompany the diurnal testosterone cycle, although the precise nature of these changes has yet to be established. Also, there is no information on how diurnal changes in oestrogen correspond to cognitive performance.

Testosterone levels have also been reported to vary in human males across seasons with levels higher in autumn and lower in the spring (Smals, Kloppenborg and Benraad, 1976). It has been hypothesised that there is an optimal level of androgen in association with sex differences in cognitive abilities. Females with higher levels of androgens will perform similarly to males who have naturally lower levels of androgens (Shute, Pellegrino, Hubert and Reynolds, 1983). Kimura (1991) supported this theory of an optimal level of androgen. She compared sex differences in spatial abilities in spring and autumn and found that the sex differences in spatial abilities favouring males were more significant during the spring than the autumn. However, hormone levels were not measured, therefore, a direct association between testosterone levels and spatial performance was not confirmed. A further study investigated influence of seasonal fluctuation of testosterone on functional asymmetry. As will be detailed later in section 1.7.2. The term *functional asymmetry* has been used to refer to left hemisphere specialisation for verbal processes and right hemisphere specialisation for non-verbal processes. The hemispheres are organised

differently for males and females. These patterns of asymmetry were exaggerated in spring (the magnitude of sex difference was greater) compared to the autumn, however, no direct association was found between seasonal testosterone concentration and functional asymmetry (Wisniewski and Nelson, 2000). Therefore, it was concluded that seasonal variations in testosterone do not directly influence seasonal changes in functional asymmetry in men and women.

Such findings tentatively suggest that some of the variability across research studying sex differences may, in part, be due to seasonal fluctuations in hormones.

1.7. Neuroanatomical differences in brain structure, organisation and function.

Hormones have a fundamental influence on the structure and organisation of the developing brain. Research also has shown how the brains of males and females are structurally different. These differences could play a role in the observed cognitive sex differences.

1.7.1. Sexually dimorphic structures in the brain: The corpus callosum

(CC)

As previously mentioned in the animal research, the CC is a collection of neural fibres that connects the two hemispheres in the brain and transfers information from one hemisphere to the other. From autopsies in humans, a region of the CC called the splenium has been suggested to be larger and more bulbous in females than in males (Allen, Richey, Chai and Gorski, 1991; Holloway and de Lacoste, 1986; Davatzikos, Vaillant, Resnick, Prince, Letovsky and Bryan, 1996). Larger callosal size has been associated with greater interhemispheric connectivity (Aboitiz, Scheibel and Zaidel, 1992). Hines (1990) reviewed the literature looking at size of the CC between males and females in humans and concluded that specific areas of the CC were larger (relative to brain weight) in females compared to males. It was suggested that the superior performance in Verbal Fluency of females might be due to this larger and thus more efficient corpus callosum in transfer of information (Hines, 1990). Data on females support this. Verbal Fluency correlates positively with the area of the splenium in women (Hines, Chiu, McAdams, Bentler and Lipcamon, 1992).

Findings of a sex difference in the CC have been constantly challenged however. Other research has not found a sex difference in the CC and has suggested other factors that may determine the size of the CC. Witelson (1985) found that the size of the CC was larger in left-handers than in right-handers. Others have proposed that sexuality determines size of CC, such that the CC is larger in homosexual males than heterosexual males (Allen and Gorski, 1992). In addition, Byne, Bleier and Houston (1988) found large variations in callosal size and shape among individuals regardless of age or gender. Subsequent research suggests that CC morphology also appears to change with age. CC size decreases with advanced age in male and female adults, while CC size increases with advanced age in children (Wisniewski, 1998). However, even when the CC of age-matched individuals was studied using MRI, sex differences in the human CC were found (Constant and Ruther, 1996). A meta-analytic review summarised 43 studies and concluded 1) left-handers do have slightly larger CC than right-handers 2) females have larger CC than males after adjusting for brain size, and 3) CC area does decrease with age (Driesen and Raz, 1995).

To summarise, whilst sex differences in the CC have been suggested these are still highly debatable. Factors such as age, brain weight, sexuality and handedness alongside the use of differing methodological (autopsy versus

MRI) and statistical procedures among studies have been suggested to produce these conflicting results among studies. There is a vast amount of research in this area. Given the abundance of inconsistencies among studies, it may be premature to conclude that reliable sex differences in the CC do exist (for an extensive discussion in this area see Collaer and Byne, in press).

1.7.2. Sex differences in hemispheric dominance and functional asymmetry.

One theory proposes that prenatal hormones assert their effect on cognition during foetal development by influencing the rate of development of the right and left cerebral hemispheres. This theory suggests that testosterone delays the neuronal development of the left hemisphere, causing the right hemisphere to develop faster than the left hemisphere (Geschwind, 1983, 1984; Geschwind and Galaburda, 1987). This results in right hemisphere dominance for cognitive abilities, which means the right hemisphere has greater control than the left hemisphere. The term *functional asymmetry* has been used to refer to left hemisphere specialisation for verbal processes and right hemisphere specialisation for non-verbal processes.

Hemisphere dominance relates also to whether someone is left or right handed, thus handedness is an indirect index of lateralisation. The left hemisphere is responsible for controlling the right side of the body and the right hemisphere controls the left side. As Geschwind's theory proposes that prenatal testosterone slows down the growth of the left hemisphere, the result would be right hemisphere dominance (and also left-handedness). The male foetus is exposed to higher levels of testosterone than the female foetus, and there is a higher rate of left-handedness in males (Bryden, 1977; Halpern, Haviland and Killian, 1998). Therefore, there is a sex difference in hand preference such that on average, the prevalence of right-handedness is higher in females than in males (Lansky, Feinstein, Peterson, 1988; Oldfield, 1971). Right-handers are almost always left-hemisphere dominant for verbal and language abilities (Hines and Gorski, 1985; Smith and Hines, 2000). In contrast, a larger proportion of left-handers are right-hemisphere dominant for verbal and language abilities (see Moffat and Hampson, 1996, for a review).

In right-handers, sex differences in functional asymmetry have been reported. Evidence for this in humans has come from research looking at the differential effect of brain lesions in males and females. It was discovered first that left hemisphere damage reduces verbal test scores,

whereas right hemisphere damage leads to a reduction in non-verbal abilities (see Mountcastle, 1962, for review). When males and females were studied separately, it was reported that the pattern of deficits demonstrated after unilateral brain lesions was dependent upon the sex of the patient and the side of the lesion. In females, the cognitive deficits produced were less severe than in males (see Gazzaniga, 1998, for review). This suggests that males have more functional asymmetry than females, for both verbal and non-verbal abilities (McGlone and Kertesz, 1973; McGlone, 1978). This is consistent with the evidence previously outlined for sex differences in these abilities and left hemisphere dominance in females and right hemisphere dominance in males.

MRI studies have also examined the functional organisation of the brain for verbal memory tasks. Shaywitz, Shaywitz, Pugh, Constable, Skudlarski, Fulbright, Bronen, Fletcher, Shankweiler, Katz and Gore (1995) studied brain activation patterns in males and females performing tasks of letter recognition (orthographic), rhyming (phonological) and semantic category (lexical-semantic judgment). They found that for males, brain activation was lateralised to the left inferior frontal gyrus regions on the phonological task only. For females, pattern of activation is very different for this task, engaging more diffuse neural systems that involve both left and right

inferior frontal gyri. This supports the hypothesis that language functions are more likely to be highly lateralised in males and to be represented in both cerebral hemispheres in females. Furthermore, Pugh, Shaywitz, Shaywitz, Constable, Skudlarski, Fulbright, Bronen, Shankweiler, Katz, Fletcher and Gore (1996) observed significant sex differences in the cerebral organization of processes involved in reading. They found greater left hemisphere dominance in phonological regions for males than for females. However, Knecht, Deppe, Draeger, Bobe, Lohmann, Ringelstein, and Henningsen (2000) also employed MRI techniques and found evidence that language lateralisation during word generation in right-handed men and women were equivalent. Furthermore no gross differences in pattern of activation between male and female subjects were found using either Verbal Fluency tasks or language comprehension tasks (Schlosser, Hutchinson, Joseffer, Rusinek, Saarimaki, Stevenson, Dewey and Brodie, 1998; Frost, Binder, Springer, Hammeke, Bellgowan, Rao, Cox, 1999). These data from MRI procedures show evidence of task-specific sex differences in the cerebral organisation of language processing.

Findings of sex differences in functional asymmetry may relate to the sex differences in brain structure described previously. The region of the CC called the splenium has been suggested to be larger and more bulbous in

females than in males and larger callosal size has been associated with greater interhemispheric connectivity. As it has been hypothesised that morphological sex differences in callosal size would produce greater interhemispheric communication in women, findings are consistent with the idea that female brains are organised for the use of both hemispheres in cognition, more so than male brains are.

1.8. Neurophysiological evidence

Neurophysiological evidence has been put forward to explain how oestrogen can influence memory and cognition, particularly for tasks that show sex differences. It has been proposed that oestrogens, and other sex steroid hormones, influence aspects of central nervous system function, such as neuronal enzyme activity and neurotransmitter uptake and turnover, which in turn may result in changes in performance (McEwen and Parson, 1982). Giving oestradiol to ovariectomised rats enhances cholinergic function, such that oestrogen increases choline acetyltransferase (CHAT), the enzyme needed to synthesise acetylcholine in basal forebrain (Luine, 1985; Farr, Banks and Morley, 2000). Furthermore, in the rat brain, the activities of choline acetyltransferase are responsive to levels of circulating

oestrogens (Luine, Khylichevskaya and McEwen, 1975; Luine, Park, Joh, Reis and McEwen, 1980). This enzyme is critical in the synthesis of acetylcholine, a major transmitter in the basal forebrain. Acetylcholine is implicated in human learning and it is suggested that its depletion may contribute to the memory disorder, Alzheimer's Disease (AD) (Simpkins, Singh and Bishop, 1994; Kopleman, 1986). Similarly, in women undergoing ovariectomy, oestrogen loss is associated with a reduction in cholinergic neuronal activity (McMillan, Singer and Dorsa, 1996). Additional evidence that the cholinergic system is involved in memory comes from reports that when an anti-cholinergic agent, Scopolamine, is administered to the cholinergic system, memory impairments result (Drachman and Leavitt, 1974). Other research on AD has located oestrogen receptors in brain areas affected by AD (Miranda, Sohrabji and Toran-Allerand, 1993). In AD, neuronal loss and neurofibrillary tangle formations are prominent in both the CA1 region of the hippocampus and in the basal forebrain. These areas have oestrogen receptors (Coyle, Price and DeLond, 1983; Hyman, Vanhoesen, Damasio and Barnes, 1984; McEwen, 2002). These findings suggest that the increased incidence of AD in older women compared to men, may be directly related to oestrogen deficiency and implicates the potential use of Oestrogen Replacement Therapy (ERT) to prevent or delay the onset of this disease (Paganini-Hill and Henderson,

1994; Simpkins et al, 1994; Kimura, 1995; McBee, Dailey, Dugan and Shumaker, 1997).

Luine's findings were suggestive of an alternative approach to treating AD – this being, to treat the deficit in AD patients with oestrogen, specifically to increase levels of the enzyme necessary for neurotransmitter synthesis. Fillit, Weinreb, Cholst, Luine, McEwen, Amador and Zabriskie (1986), examined this idea through a preliminary trial to assess safety and potential effectiveness of low-dose oestradiol therapy in postmenopausal women with Senile Dementia-Alzheimer's type (SDAT). Of the seven women treated with low dosages of oestradiol over a six-week period, significant improvements in three women were noted on measures of attention. In addition, when 15 women with AD were treated with oestrogen for six weeks, they improved their scores on the MMSE, compared to a control group of women with AD, matched for age and severity of dementia (Ohkura, Isse, Akazawa, Hamamoto, Yaoi and Hagino, 1994). However, other researchers have investigated the benefit of ERT for the treatment to women with mild to moderate AD and found that oestrogen failed to improve short-term cognitive or functional outcomes (Mulnard, Cotman, Kawas, van Dyck, Sano, Doody, Koss, Pfeiffer, Jin, Gamst, Grundman Thomas and Thal, 2000; Henderson, Paganini-Hill, Miller, Elble, Reyes,

Shoupe, McCleary, Klein, Hake and Farlow, 2000). This does not however rule out long-term beneficial effects. Indeed it has been reported that in older women who were all diagnosed with memory impairments of SDAT, non oestrogen users deteriorated significantly from baseline to a follow up of one year as assessed by the Blessed-Roth Dementia Scale. Oestrogen users however had higher cognitive functioning at baseline and follow-up. These results were similar in groups matched on baseline Blessed-Roth Dementia Rating Scale ratings (Costa, Reus, Wolkowitz, Manfredi and Lieberman, 1999). These studies suggest that ERT may be of value in improving the cognitive disturbances in SDAT patients. However, recent research suggests caution in generalising the beneficial effects of ERT on cognition, to other types of hormone therapy given to older women. An increased risk of cognitive decline and probable dementia occurred in older women taking oestrogen plus progesterone, compared to placebo controls. Furthermore, cognitive enhancements were not seen in association with this hormone treatment (Rapp, Espeland, Shumaker, Henderson, Brunner, Manson, Gass, Stefanick, Lane, Hays, Johnson, Coker, Dailey and Bowen, 2003; Shumaker, Legault, Rapp, Thal, Wallace, Ockene, Hendrix, Jones, Assaf, Jackson, Kotchen, Wassertheil-Smoller and Wactawski-Wende, 2003). These studies recruited women from the Women's Health Initiative (WHI) hormone therapy trials that, as previously mentioned, were

discontinued because women in the oestrogen plus progesterone were at increased risk for heart disease, stroke, pulmonary embolism and breast cancer. As such adverse side effects in the women taking oestrogen only were not found, an additional 3,000 women remain in this large-scale study. Results will be of interest to determine whether it is the added progesterone to ERT that contributes to the increased risk of dementia.

1.9. Confounding variables in sex research.

As stated earlier, there are within sex differences in memory and cognition. Research has identified factors other than sex that are associated with performance. These include handedness (as outlined earlier), mood, age, sexual orientation, diurnal and circannual influences and alcohol or nicotine use. Where possible these factors should be controlled for in research into hormonal influences on cognition. There are also further considerations in sex research such as sex of researcher, experimenter/participant bias, date of publication, situational variables and publication bias. Each of these will be outlined in the subsequent sections. These considerations affect all areas of research, not specifically the present research.

1.9.1. Mood

Memory and cognitive performance may be altered due to mood (Hackman and Galbraith, 1976). A resource allocation model has been developed to explain disruptive effects of mood on memory and cognition (Ellis and Ashbrook, 1988). This assumes that encoding of information requires some allocation of cognitive capacity or effort. Emotional states regulate the amount of capacity available to be allocated to the cognitive task. Most cognitive tasks involve information that requires some allocation of capacity, therefore distressing mood state is said to reduce the total capacity for processing the task in question. Memory performance has been shown to correlate with amount of capacity allocated to the cognitive task (Ellis, Thomas and Rodriguez, 1984). Furthermore, mood effects are less prominent when the to-be-remembered information is organised into a coherent, integrated theme, rather than consisting of relatively isolated units of information (Ellis, Thomas, McFarland and Lane, 1985). Also of relevance, is the type of cognitive task. In a study of the effects of a depressed mood induction on the recall of low and high effort materials, depressed subjects were poorer in recall of the high effort materials, yet recall was not impaired with the recall of the low effort materials. Relating this to the resource allocation model, Ellis and Ashbrook (1988) propose

that depressed mood states impair performance on difficult tasks, because such tasks make heavier demands on capacity for encoding. This could explain how depression does not interfere with automatised activities, which do not themselves consume attentional resources.

Additional evidence that changes in mood are especially relevant to performance on cognitive tasks comes from a study that looked at mood and cognition over the menstrual cycle. A significant association was found between depressed mood and perceptual asymmetry on a face perception task, suggesting that depressed mood negatively affects performance of this task involving the right hemisphere (Compton and Levine, 1997). In addition, a symptom of depression is lack of concentration. Therefore depressed mood may confound research focusing on sex differences in cognition.

The effect of arousal on memory has also been addressed, in the context of anxiety. The Yerkes-Dodson law (Yerkes and Dodson, 1908) says that high emotional arousal restricts the deployment of attentional capacity – similar to predictions made by the resource allocation model. To compliment this, the ‘test anxiety’ literature claims that the cognitive component of anxiety (worry) is disruptive and debilitating to recall, presumably because it takes

up attention and thus distracts (Morris and Liebert, 1970; Sarason, 1975). The arousal component of anxiety (emotionality) appears to have little, if any, effect on performance (Sarason, 1980).

It has been suggested that mood is influenced by hormones.

For instance, the dramatic decline in oestrogen levels following delivery has been implicated as a possible cause for 'maternity blues' or postnatal depression (Harris, 1996). An abundance of research however has focused on postmenopausal women who may suffer depression or anxiety as a result of oestrogen deficiency. Another opportunity to study the influence of hormones on mood has been through menstrual cycle studies. In addition, the influence of hormones on mood in men and circannual and diurnal influences of hormones on mood have also been studied.

Postmenopausal women and mood

Reports have demonstrated an improvement in mood in association with ERT. Low levels of oestrogen treatment have been associated with depressive feelings and anxiety in postmenopausal women (Ditkoff, Cracy, Cristo and Lobo, 1991; Klaiber, Broverman, Vogel and Kobayashi, 1979; Boyle and Murrihy, 2001; see Halbreich, 1997 for review). More recently, a beneficial response to oestrogen in women suffering with clinically

diagnosed depression was found. In this study all women were taking fluoxetine (an anti-depressant medication). A sub-section of this group was also taking ERT. Those taking ERT alongside fluoxetine showed a significant reduction in depressive feelings when compared with those only taking fluoxetine (Schneider, Small, Hamilton, Bystritsky, Nemeroff, and Meyers, 1997). However, these findings were not confirmed elsewhere (Amsterdam, Garcia-Espana, Fawcett, Quitin, Reimherr, Rosenbaum and Beasley, 1999). It has been suggested that more research is needed to guide how oestrogen may be given to those who fail to respond to anti-depressants (Stahl, 1998).

A meta-analytic review was performed to ascertain the overall effect of HRT upon depressed mood, whilst considering several moderator variables that could be responsible for differences among studies. This found a significant reduction in depressed mood in association with HRT. Furthermore, different hormone preparations used across the studies led to some variability. For ERT only preparations, the Effect Size (ES) for mood improvement was .69¹ indicating that those receiving treatment had lower levels of depressed mood than control patients. (P) only and combined EP

¹ Effect Size was calculated by dividing the difference between the 2 group means by the pooled standard deviation (Cohen, 1969). Higher ES reflects a better mood.

reduced the ES to .39 and .45, respectively. (A) only and combined Oestrogen and Androgen (EA) preparations increased the ES to 1.37 and .90, respectively. Differences in length of treatment and the measures used to assess changes in depression also produced variability in ESs calculated (Zweifel and O'Brien, 1997). Supporting the findings of this review it has been suggested that the addition of progesterone in some combined forms of HRT may oppose some of the beneficial effects of oestrogen on mood (Sherwin, 1991). However, a study conducted after the meta-analysis comparing women on the combined treatment versus those on oestrogen treatment only, found no differences between these two groups for mood. Where a positive association between HRT and mood was found in one subgroup that were aware of the purpose of the study, this was not replicated in a second subgroup who were not aware of the purpose of the study. The authors concluded that any reported mood enhancements in the first subgroup might be due to expectancy of positive HRT effects on mood (Hogervorst, Boshuisen, Riedel, Willeken and Jolles, 1999).

It has been proposed that oestrogen alleviates depressed mood among menopausal women by increasing serotonin levels, which subsequently

decreases monoamine oxidase activity (MAO) ² (Sherwin and Gelfand, 1985). Klaiber, Broverman, Vogel, Peterson and Snyder (1997) employed a double-blind, placebo-controlled, cross-over design to compare the same women over five monthly cycles receiving different preparations of HRT (either ERT or EP). Women in the group were distinguished by duration of menopause – short versus long. All women showed mood improvement when taking ERT and significant mood impairment when taking EP. However, those who were characterised by both long duration of menopause and lower levels of pre-treatment serum oestradiol were significantly more dysphoric when receiving EP, compared with those women receiving EP, who were characterised by both short duration of menopause and higher levels of pre-treatment serum oestradiol. Furthermore MAO levels negatively correlated with oestradiol levels during the HRT. It is suggested that longer duration oestrogen deficiency may lead to an impairment of oestradiol receptor function leading to a greater impact of the negative effects of progesterone. As outlined earlier, not all women respond negatively to EP preparations and the authors further identify factors other than duration of menopause and type of preparation, which lead to individual differences in mood response to EP

² Monoamine oxidase inhibitors are drugs used in the effective relief of depression and work by increasing the neurotransmitter serotonin. A widely accepted hypothesis is that depression is associated with a deficiency of serotonin.

preparations. Low pre-treatment levels of gonadal hormones, low MAO activity and pre-treatment mood disorders distinguished the longer duration group of menopausal women from the shorter duration group.

Similar to the previous meta-analytic findings, Sherwin (1991) reported that a combination of oestrogen and androgen was superior to oestrogen alone in elevating mood in recently oophorectomised women. However, inconsistencies across studies persist as a direct association between oestrogen and improved mood has not always been found. Barrett-Connor, von Muhlen, Laughlin and Kripke (1999) studied plasma levels of oestradiol, testosterone, estrone, androstenedione, cortisol, dehydroepiandrosterone (DHEA) and Dehydroepiandrosterone Sulfate (DHEAS) in postmenopausal women. They found that only the androgen, DHEA was inversely associated with depressed mood, such that the lower the level of DHEA the higher the depression scores on the Beck Depression Inventory (BDI). See Table 3 for a summary of past research involving mood and HRT in women.

Menstrual cycle and mood

Premenstrual depression can occur in women before menstruation leading to tension, fatigability, difficulty in concentration and reduced sexual

interest (O'Brien, 1993). It has been suggested that in the midluteal phase, when oestrogen levels are high and progesterone peaks, there is an enhancement of mood, while the reverse occurs at menses, when oestrogen and progesterone levels are low, however mood changes in association with these hormonal fluctuations across the menstrual cycle are not reliable and remain debatable (Maki, Rich and Rosenbaum, 2002; Compton and Levine, 1997; see Friedman, Hurt, Arnoff and Clarkin, 1980, for a review).

Hormones and mood in men

Oestradiol therapy has been given to male patients who have dementia. One symptom of dementia can be aggressive behaviour, which is one of the most difficult problems caregivers suffer. One paper describes how four male patients with dementia were administered therapeutic low doses of oestradiol. Within one to three days, aggressive behaviour decreased and their mood was improved (Kay, Yurkow, Forman, Chopra and Cavalieri, 1995). One benefit of this treatment is the lack of side effects from more conventional drugs given to reduce aggressive behaviours³. Such side effects include Parkinsonism, Tardive Dyskinesia and postural hypertension.

Another group of researchers has looked at the effects of testosterone therapy in the treatment for men who are HIV positive. One common disorder associated with this syndrome is clinical hypogonadism. This involves low levels of testosterone leading to low libido, alongside other associated symptoms such as depression, fatigue and weight loss. In one study, Testosterone Replacement Therapy (TRT) was given to these men. 79% responded positively to this treatment in terms of mood and energy levels (Wagner, Rabkin and Rabkin, 1998). See Table 4 for a summary of past research involving men and HRT.

Circannual changes in mood

It has been suggested that mood is related to the time of year. This relates to the lay man term 'Winter Blues', which has been labelled as Seasonal Affective Disorder (SAD) (Rosenthal, Sack, Gillan, Lewy, Goodwin, Davenport, Mueller, Newsome and Wehr, 1984). This disorder is characterised by negative depressive mood during the autumn and winter months with remission in the spring and summer months. It is thought that lack of daylight is the cause of this disorder and light therapy has been

³Conventional drugs given to those suffering dementia include major tranquilisers, also known as neuroleptics or anti-psychotics. These are used to control agitation and aggression. Commonly used drugs are thioridazine (Melleril) and halperidol (Serenace).

given to relieve these symptoms (Terman, Terman, Quitkin, McGrath, Stewart and Rafferty, 1989).

The evidence presented in this section suggests that mood can be influenced by hormones and also that mood influences cognition. Therefore, mood might be a confounding influence in research looking into hormonal effects on cognition. In the research presented in this thesis, mood might introduce a source of systematic error in the data. Therefore, mood will be measured to ascertain any possible relationships between mood and cognition.

1.9.2. Age

Age related differences in memory are important, particularly when studying populations cross-sectionally. Such research has used an information-processing model (Murdock, 1967). This assumes that information can be traced through several hypothetical memory stores: A modality-specific sensory memory, a short-term primary memory and a long-term, secondary memory (a repository of newly learned information). Permanent or remote information is stored in a tertiary memory. These distinctions help to classify findings. With the exception of response time,

primary memory is relatively unaffected by age. However, in the Digit Span test (a verbal, working memory task, assessing attentional skills), if the subject is required to recall the list immediately, older people, on average, recall slightly fewer digits than younger people. Also, if the list has to be recalled in reverse order, the older person (over approximately forty-five years) is at more of a disadvantage than the younger person (Bromley, 1958). Comparatively larger age differences are found when secondary, memory processes are involved. Gilbert and Levee (1971) found slight age differences in Digit Span but substantial age differences for PAL, designs and paragraph recall. It also has been reported that older adults exhibit slower acquisition rates in PAL (Jerome, 1959; Winn, Elias and Marshall, 1976).

Memory differences have been explained by biological changes during aging. Neurochemical and pharmacological work on peptide and cholinergic drugs, with both animal and human subjects, have shown that changes in neurotransmitter and neuroendocrine functions in the later years of healthy individuals, could be responsible for some of the decline observed in cognitive functions (Hines, Poon, Cerella and Fozard, 1983). Administration of an acetylcholine antagonist – a receptor blocker – resulted in reduced memory performance in young adults, similar to that

observed in the elderly. This condition can be reversed with the administration of acetylcholine agonist.

The evidence presented in this section suggests that age can influence cognition. Further hormone levels change with age, e.g., oestrogen levels decline during the menopause. Therefore, systematic error might be introduced in the data if a relationship between age and cognitive performance was found. In a between subjects design, if the control group was significantly older than the experimental group, or vice-versa, and the older group performed differently on cognitive tasks to the younger group, then age would be a systematic source of error confounding hormonal effects on cognitive performance. To compensate for this influence in the research presented in this thesis, possible relationships between age and performance will be explored. Also, the third study (Chapter 4) uses two groups that are tested twice. One group tested once off hormone treatment and then tested later when on hormone treatment. The opposite is true for the second group who are tested once whilst on hormone treatment and then tested later when off hormone treatment. Therefore, this design automatically controls for systematic age effects.

1.9.3. Sexual orientation

There is growing research that suggests that sexual orientation relates to patterns of cognitive abilities. This relates to animal studies, which suggest that prenatal hormones influence the development of all characteristics that show sex differences, including sexual behaviour, as well as cognitive functioning. Changes in sexual behaviour due to neonatal castration of male animals or to perinatal testosterone administration to females have been reviewed. In several species these techniques lead to sexual behavior with other animals of the same sex (Adkins-Regan, 1988). In addition, gonadal hormones influence certain aspects of cognitive performance that show sex differences in rodents, particularly spatial memory (Refer to previous section 1.5. regarding evidence for gonadal hormone influences on cognitive abilities in animals).

As previously mentioned, it is generally accepted that on average males excel at certain visual-spatial tasks, while on average females excel at certain verbal abilities. As there is overlap between the sexes in these abilities it has been proposed that sexual orientation in humans may explain some of this within-sex variability. It has been hypothesised that prenatal hormones affect sexuality in humans, which, may in turn, be associated

with patterns of cognitive sex differences, such that male homosexuals are more similar to female heterosexuals in cognitive pattern and female homosexuals are more similar to male heterosexuals. This conjecture was supported with findings that homosexual men performed more similarly to heterosexual women on spatial and verbal abilities that show reliable sex differences (Gladue, Beatty, Larson and Staton, 1990; Kimura, 1996; Hall and Kimura, 1995; Sanders and Wright, 1997; Wegesin, 1998; Neave, Menaged and Weightman, 1999). However, some studies have reported that sexual orientation was not related to performance on various sexually dimorphic cognitive measures in homosexual males and homosexual females (Gladue and Bailey, 1995; Tuttle and Pillard, 1991). Further there have been very few reports of a similar pattern in homosexual females. Gladue et al (1990) reported that heterosexual females and homosexual females did not perform any differently on a female favouring verbal task and in fact, homosexual females performed significantly worse on a male favouring spatial task. These findings were confirmed elsewhere (Gladue and Bailey, 1995; Tuttle and Pillard, 1991).

Sexual orientation and handedness

One possible explanation for some of the inconsistencies between studies may be due to the additional confounding factor of handedness. As

previously mentioned handedness is a measure of hemispheric dominance (Refer to 1.7.2. regarding sex differences in hemispheric dominance and functional asymmetry). McCormick and Witelson (1991) reported sex differences in cognitive abilities for both left and right-handers but the effects of sexual orientation on cognitive performance were only observed in right-handed participants. However, the relationship between handedness, sexual orientation and cognitive performance remains putative. Some researchers have reported a greater incidence of left-handedness in homosexual men and homosexual women (Lindesay, 1987; McCormick, Witelson and Kingstone, 1990) while others have not (Gladue and Bailey, 1995; Marchant-Haycox, McManus and Wilson, 1991; Willmott and Brierley, 1984). A further explanation that might reconcile inconsistencies between studies regarding the relationship between sexual orientation and cognitive pattern is that the studies outlined used different measures, therefore of importance might be the precise nature of the task and the magnitude of sex difference the task reliably shows.

The evidence presented in this section suggests that a person's sexual orientation may influence sexually dimorphic cognitive abilities. In the studies presented in this thesis, it is unlikely that the experimental groups differ systematically in their sexual orientation, as this occurs randomly in

groups. Therefore, sexual orientation as a potential confounding variable might introduce a source of random error in the data. However, in a between subjects design, if one of the groups was predominantly homosexual and the other group was predominantly heterosexual, any between group difference in cognitive performance, might be systematically influenced by the confounding sexual orientation of the group, rather than hormones. Further, sexual orientation does not change for a given individual, therefore the repeated measures design in the third study in this thesis (Chapter 4), would not have systematic bias.

1.9.4. The effects of time of day and year on memory, mood and cognition

As previously mentioned, it is suggested that the time of day and year may influence hormone levels with its subsequent influence on memory and cognition. Further, evidence has been outlined to suggest that mood is influenced by circannual changes. Therefore, where possible research studying mood, memory and cognition might need to control for time of day and year.

For the studies in this present thesis, both the control and the experimental groups were tested when they were available and not assigned to a specific time of day or year, therefore possible confounding variables such as time of day or year are more likely to introduce random error, rather than systematic error, to the data.

1.9.5. Alcohol and hormone levels

Severe alcohol abuse is directly related to the memory disorder, Korsakoff's Syndrome. In addition, more moderate alcohol use could affect memory by altering hormone levels. Gill (2000), reviewed studies of moderate alcohol intake in premenopausal and postmenopausal women and concluded that alcohol caused an elevation in oestrogen levels in women. Thus, some of the inconsistencies in research into pre, peri and postmenopausal women, may be due to lack of control over individual differences in alcohol consumption.

The evidence presented in this section suggests that alcohol may influence hormone levels. Evidence suggested that hormone levels may influence cognition. In the research presented in this thesis, the experimental groups are not likely to be more influenced by heavy alcohol use than the control

groups, or vice-versa. Therefore, this possible confounding influence is not likely to influence the outcome. Where possible, alcohol use should be recorded to ascertain any possible influence on cognitive scores.

1.9.6. Nicotine and cognitive performance

Research focusing on the effects of nicotine on cognitive behaviour has compared smokers with non-smokers on general academic performance. Smokers performed higher than non-smokers in general academic success (Warburton, Wesnes and Revell, 1984). The immediate effects of nicotine on performance have also been studied in smokers and non-smokers. Smoking has been associated with improvements on Verbal PAL, paragraph recall and free recall (Mangan, 1983; Wesnes and Warburton, 1984; Rusted, Graupner and Warburton, 1995; Warburton and Arnall, 1994). Further support of these beneficial effects have been demonstrated in patients with Alzheimer's Disease, where administration of subcutaneous nicotine has been associated with attentional improvements in both smokers and non-smokers (Jones, Sahakian, Levy, Warburton and Gray, 1992). It has been proposed that smoking improves mental efficiency in tasks involving concentration and information processing in the brain (Wesnes and Warburton, 1983). Thus, another source of variability in

studies involving cognition may be individual differences in nicotine consumption.

The evidence presented in this section suggests that nicotine may influence cognitive performance. In the research presented in this thesis, the experimental groups are not likely to be more influenced by nicotine withdrawal use than the control groups, or vice-versa. Therefore, this possible confounding influence is not likely to influence the outcome. Where possible nicotine use should be recorded to ascertain any possible influence on cognitive scores.

1.10. Considerations in sex difference research

There are a number of factors to consider when taking an overview of the literature in this field.

1.10.1. Sex of Researcher and experimenter/participant bias.

This is a possible bias in sex difference research. For example, a male researcher may hold a particular agenda for finding a sex difference favouring males and vice-versa for female researchers. This inclination may be conscious or unconscious but can alter performance of the participant leading to demand characteristics. Orne (1962) described this influence as ‘the totality of cues (verbal or non-verbal) which appear to reveal the experimental hypothesis and which tell the participant what is required of her or him’. This can also alter the perceptions of researchers. Rosenthal (1966) reported how students that were given groups of ‘bright’ and ‘dull’ rats (who were actually randomly mixed for ‘brightness’) produced results consistent with the label of the rats. This is of importance since a major foundation for sex difference research in humans has come from rat studies. Indeed similar effects have been seen in studies of human beings. Teachers were told that their students were either high or low achievers (all students were randomly allocated to these groups).

Subsequently children produced IQ scores consistent with the teachers' expectations (Rosenthal and Jacobson, 1968).

1.10.2. Date of Publication

It is possible that sex differences in cognition and memory may disappear or increase over time, implicating an environmental explanation as influential in how males and females might perform differently. An example may be how boys and girls may be encouraged via teaching practices to excel in different disciplines. Such teaching practices may change over the years. Therefore, it is important to consider the year of publication when reviewing research findings.

1.10.3. Situational variables

People may alter their behaviour according to the situation they may be in. For example, people may perform differently with same-sex versus opposite-sex researchers, as well as with naturalistic versus unnaturalistic settings. Where possible all participants in research should be exposed to the same, or similar, situational settings.

1.10.4. Publication bias and Meta-analyses

Due to limited space in journals, peer reviewers have a tendency to accept research for publication that yields positive findings, such as those that show sex differences. This is a general problem that positive findings are more likely than negative findings to be published. Over publication of positive results poses a practical problem for meta-analyses. Meta-analysis is a statistical procedure, which attempts to summarise the research literature from one area from all individual studies. This aids the researcher to summarise a large number of individual research studies and to estimate the magnitude of sex difference across studies (Rosenthal, 1984). While this is useful, this technique has been criticised for over-representing published, positive findings and under-representing, unpublished, negative findings. This is also known as the 'file-drawer problem' (Rosenthal, 1979). This refers to all the studies that found negative findings and were never published (i.e., are still in the file drawer). Thus it is important to consider when interpreting findings that the magnitude of a sex difference from past, published research may be inflated or that single reports of a sex difference may be spurious.

1.11. Transsexualism

It has been previously outlined in rat studies how cross-sex hormones have been administered and the effect on spatial performance has been observed. Ethical considerations make it difficult, or impossible, to conduct similar experimental studies in humans. However some information on how hormones influence human cognition or memory has come from situations where people are given hormones for other reasons. One such situation is transsexualism, or gender dysphoria.

Individuals with transsexualism feel they were born with the wrong body. Males feel they should have been born females and vice versa. As part of their treatment, they are given cross-sex hormones. Transsexualism is a psychological disorder. The diagnostic criteria normally used for diagnosing transsexualism (often termed 'Gender Identity Disorder' – GID - by psychiatrists) are laid down in the American Psychiatric Association's Diagnostic and Statistical Manual, 4th edition, text revision (referred to as DSM-IV-TR). In summary, the key features are: 1) A strong and persistent cross gender identification; 2) Persistent discomfort with their assigned natal sex and its associated gender role; 3) Absence of any physical intersex condition; and 4) Clinically significant distress or impairment of

social or occupational functioning. Transsexuals are not delusional as that do not really believe they are the opposite sex, however their gender identity is at conflict with their physical sex. Medical treatment may be sought to help overcome this psychological disorder. Transsexuals may be genetically born males or females. A Male-to Female (M-F) transsexual is a genetic male who feels he is a female. A Female-to-Male (F-M) transsexual is a genetic female who feels she is a male. Although the occurrence of transsexualism varies across the world, in England, the estimated prevalence of M-F transsexuals has been 1:34 000, whereas the estimated prevalence of F-M transsexuals has been 1:108 000 England (Hoenig and Kenna, 1974). Similar prevalence rates have been reported elsewhere (Walinder, 1971). More recent data has agreed with these prevalence rates. The DSM-IV-TR states that 1:30, 000 men seek sex re-assignment surgery (SRS) and 1: 100,000 women seek SRS (American Psychiatric Association, 2000). In the Netherlands, prevalence rates are higher with about 1:20,000 men and 1:50,000 women that seek treatment for GID (Gooren, 1990). It is likely however that the prevalence of GID is higher as some people may be gender dysphoric but not wish to pursue sex re-assignment.

After diagnosis M-F transsexuals are prescribed cross-sex hormone therapy to acquire female secondary characteristics such as breast development. Concurrently they are expected to work and live in their chosen gender role. This is referred to as the real life experience. After two years in their chosen gender role, of which a year has to include working or studying, they may be referred for surgical gender re-assignment. For M-F transsexuals, Sex Reassignment Surgery (SRS) involves either a vaginoplasty⁴ or colovaginoplasty⁵.

Studies examining chromosomal pattern, genitals or circulating and peripheral gonadal hormones in transsexuals, have not shown any distinguishing features from other individuals who share the same sex, but are not gender dysphoric (Gooren, 1990). A question as to the aetiology of transsexualism remains however. It has been proposed that transsexualism can be considered as a neuro-developmental condition of the brain. This is based on research that focuses on a part of the brain located in the hypothalamus, the central subdivision of the bed nucleus of the stria terminalis (BSTc), which becomes sexually dimorphic in appearance by

⁴ This involves turning the penile skin inside out and using it to line a vaginal cavity created by blunt dissection through the muscles of the perineal area. The penis and testes are removed and labia are constructed from scrotal tissue.

early adulthood. The volume of this particular nucleus is approximately twice the size in males than it is in females and is not influenced by sexual orientation. Several studies support this gender difference in BSTc volume (Zhou, Hofman, Gooren and Swaab, 1995; Kruijver, Zhou, Pool, Hofman, Gooren and Swaab, 2000; Chung, De Vries and Swaab, 2002).

Due to its tiny area post mortem studies of the brain are currently the only technique available for studying the BSTc. Of interest has been whether transsexuals differ from non-gender dysphoric male and females in BSTc size. The first study to examine this issue involved post mortem examination of six M-F transsexual brains. These transsexuals had all been treated with oestrogens in adulthood. A smaller BSTc, similar to the size found in non-gender dysphoric females was found in these transsexuals (Zhou et al, 1995). These findings were not influenced by sexual orientation. Whilst the findings suggested that M-F transsexuals develop prenatally in a way more similar to females than to males, activational influences of gonadal hormones on BSTc size cannot be ruled out, particularly as all transsexuals, apart from one, had been orchidectomised and had received oestrogen treatment. Two other men in this study who

⁵ This method is used in patients who lack sufficient material for the penile inversion method. The same method as for penile inversion vaginoplasty is followed, but instead of using penile/scrotal tissue to line the vagina, a section of the colon is isolated and used to form the vaginal lining.

were non-gender dysphoric had been orchidectomised and the size of their BSTc was in the range of the normal male, however these two men had not received oestrogen treatment. Therefore, a female-sized BSTc may be as a result of the cross-sex hormone treatment.

A second piece of research also used data collected from post mortems to examine BSTc volume in the brains of forty-two humans (Kruijver et al, 2000). Eight individuals were gender dyphoric. Of these, six were M-F transsexuals that had undergone cross-sex hormone treatment and sex re-assignment surgery (SRS), one was a M-F transsexual and had undergone no cross-sex hormone treatment and, one was a F-M transsexual. The other thirty-four non-gender dysphoric controls were grouped by sex and sexual orientation. Supporting the previous findings, sexual orientation did not influence BSTc size. Men had approximately twice as many somatostatin-expressing neurons (SOM)⁶ than women. SOM neuron count in M-F transsexuals was similar to other women, whereas SOM neuron count in the F-M transsexual was similar to other men. Variations in levels of oestrogen, testosterone, anti-androgen treatments and orchidectomy were also examined and BSTc volume was not affected by these different hormonal interventions.

⁶ Somatostatin-expressing neurons are the main neuron type in the BSTc.

Whilst these studies suggest that sex differentiation of the brain in transsexuals may be in the opposite direction to their genetic sex, few transsexuals were studied and replication, using larger samples and where possible with no hormone interventions involved, would indeed be informative.

A recent study was carried out to determine whether the sex difference in BSTc volume and SOM count appears before birth or whether the difference is due to other factors during development. Chung et al (2002) examined twenty-five male and twenty-five female human brains at autopsy, between the ages of 3 months and 49 years. These researchers were interested in the age at which the BSTc shows a sex difference in volume. Findings confirmed that BSTc size was larger in males and contained more SOMs than females, however this difference was only significant in adulthood. Findings might suggest that the human BSTc becomes sexually dimorphic at approximately puberty. The authors conclude that any hormone-induced changes in brain structure are not limited to childhood and may extend into adulthood (Chung et al, 2002).

Transsexuals offer one of the few ethical opportunities for studying the activational effects of cross-sex hormones in humans. Previous findings

reported that after 3 months of cross-sex hormone treatment (oestrogens and anti-androgens), M-F transsexuals show impairment on the 2-d Card Rotations, a visual-spatial task favouring males. Further, this visual-spatial impairment coincided with an improvement on a word production test, a Verbal Fluency task favouring females. Conversely, after 3 months of cross-sex hormone treatment (testosterone), F-M transsexuals show improvement in the Card Rotations test, coinciding with a deterioration in word production performance (Van Goozen, Cohen-Kettenis, Gooren, Frijda and Van de Poll, 1995).

Whilst these findings suggests that any organisational influences of sex hormones on sexually-dimorphic cognitive abilities in humans, may be reversed by activational influences of sex hormones, subsequent research has not found consistent findings in another transsexual population receiving similar cross-sex hormone treatment. These transsexuals underwent a battery of cognitive tests, including those tasks that were used in the former study and some additional tasks that had previously shown sex differences. Testosterone administered to F-M transsexuals for 3 months had an enhancing effect on 3-d Mental Rotation performance, but performance did not change on the 2-d Card Rotations task. Further, the spatial performance in M-F transsexuals remained stable throughout the 3

months. No change in performance was seen on the other verbal or spatial tasks as a result of cross-sex hormone treatment in either of the two groups. After long-term hormone administration (10 months), F-M transsexuals also performed better on 3-d Mental Rotations compared to baseline, although their performance was not further enhanced compared to their performance at 3 months. No change was seen on any other cognitive measure. M-F transsexuals again remained stable on all cognitive measures compared to baseline. In a subgroup of transsexuals who were withdrawn from hormone treatment for 5 weeks prior to SRS, the F-M transsexuals outscored the M-F transsexuals in 3-d Mental Rotations and their performance did not deteriorate as a result of testosterone withdrawal. Therefore, the withdrawal of hormones did not quickly reverse the activational effects on the spatial ability previously observed. The authors conclude that failure to replicate their previous findings may be due to the different test versions used and probable practise effects. Further the hormone withdrawal period may not have been sufficiently long to observe any cognitive changes (Slabbekoorn, Van Goozen, Megens, Gooren, Cohen-Kettenis, 1999).

A recent study examined the effects of cross-sex hormone treatment in a population consisting of homosexual transsexuals only. The notion in mind

was that homosexual transsexuals differ from non-homosexual transsexuals in that they may be prenatally exposed to sex hormones during critical stages of brain development, in a different way to non-homosexual transsexuals. It was predicted that homosexual transsexuals would show organising effects of sex hormones and would be less susceptible to possible activational effects that were detected in the earlier studies. Visual spatial ability was assessed using tasks favouring males, such as Line Orientation, 2-d Card Rotations, 3-d Mental Rotations, 3-d same/different and targeted throwing. As predicted, after 14 weeks of cross-sex hormone administration in both M-F and F-M transsexuals, no activational effects on any of the spatial abilities were found (Van Goozen, Slabbekoorn, Gooren, Sanders and Cohen-Kettenis, 2002). This might explain why there have been inconsistent findings in previous research that has used mixed populations of homosexual and non-homosexual transsexuals. See Table 4 for a summary of research involving men and hormone treatment.

1.12. Summary

Evidence has been presented that both organisational and activational influences of sex hormones lead to the differentiation of sexual and reproductive behaviours in male and female animals. In animals and humans sex differences have been identified in specific memory and cognitive abilities. Biological theorists propose that these sexually dimorphic abilities are due, in part, to similar organisational and activational influences of sex hormones. Structural differences in the brains of male and female rats have been identified and can be altered by administration of sex hormones. It is suggested these sex differences are organised in the brain and are said to contribute to the observed sex differences in behaviour alongside the activational effects of hormones at puberty (Collaer and Hines, 1995).

Prenatal and perinatal hormones play a critical role in brain development and subsequent sex-typical memory and cognitive abilities. In rats, performance on spatial memory tasks (that typically favour males) is subject to organisational influence of hormones. Cross-sex hormones administered neonatally produce opposite-sex performance in spatial memory. Testosterone administered to neonatal female rats masculinises

(and thus improves) performance on spatial memory in newborn female rats. Oestrogen administered to female rats prenatally or neonatally also masculinises (and thus enhances) performance in spatial memory in female rats. Activational effects of oestrogen also typically masculinise spatial memory in female rats in adulthood. This masculinisation is hypothesised to be dependent on the aromatisation of testosterone to oestradiol. These findings are not entirely consistent however and future research will discover perhaps procedural or methodological factors among studies that might explain these inconsistencies. Although the exact nature of oestrogenic influence on spatial memory is yet to be established, findings from animal studies suggest that tasks that show reliable sex differences may be more sensitive to oestrogenic change than tasks that do not show sex differences.

Research into organisational influences of sex hormones on memory and cognitive abilities are not as clear-cut in humans as they are in animals. Research has focused on individuals who have been exposed to abnormal hormone environments prenatally or neonatally (e.g., those exposed to DES prenatally and those with CAH). Whilst there is little evidence to suggest that early exposure of oestrogen influences cognitive development, there is some evidence, albeit inconsistent, that the early presence of androgens

may organise the brain to enhance certain spatial functions that show sex differences favouring males.

Research into activational influences of sex hormones on memory and cognitive abilities have mainly concentrated on the menopause and the menstrual cycle. The evidence suggests that both exogenous hormones (via ERT), and endogenous hormones (via naturally occurring fluctuations of oestrogen and progesterone during the menstrual cycle), may influence specific types of memory and cognition that show sex differences. Results are inconsistent however and as with findings from animal studies, the nature of oestrogenic change is not completely understood. Where positive influences of oestrogenic influence on memory and cognition are found, the classifications used in memory theory, such as abilities that test short-term or long-term memory have not been useful in classifying oestrogenic influences on memory. The hypothesis that oestrogen only influences tasks that show sex differences has also not been consistently supported. This may be due to inconsistent findings of whether these tasks show reliable sex differences. Inconsistent findings of hormonal influences on memory and cognition in humans among studies are thought to be due to an interaction of non-hormonal factors, which have been identified. These factors are also thought to influence memory and cognition and may also

be influenced by sex hormones (e.g., variation in the time of day, the season of year, mood and age of participants, handedness and sexual orientation).

Hormone-related variations in cognitive function appear also in men. Although the evidence is mainly correlational in nature, particular aspects of visual memory are associated with higher oestrogen levels. Testosterone replacements given to older men to raise levels comparable to younger men have been associated with improvements in memory, suggesting possible activational influences on memory. Little is known about possible activational influences of oestrogen on memory and cognition in males.

Cross-sex hormone therapy is given to M-F transsexuals and this provides researchers with a paradigm to monitor possible activational effects of oestrogen on memory, cognition and mood in genetic men. Short-term treatment with oestrogen has shown impairments on tasks favouring males and enhancements on tasks favouring females. This finding was not later replicated in another group of M-F transsexuals however. More research is needed in this area before definitive conclusions can be reached. The present research will advance understanding in the field of the effects of sex hormones on memory, cognition and mood in men. Such research will

ascertain whether activational influences of hormones on memory, cognition and mood can occur in men and whether these effects are similar to those found in women undergoing HRT. The present research can further ascertain whether any activational influences of hormones on memory, cognition and mood, can be easily reversed when hormones have been withdrawn as a pre-requisite to SRS, or whether the effects of hormone treatment on memory and cognition are longer lasting. This research will also be able to examine whether any hormonal influence on memory and cognition, if observed, is limited to those tasks that are sexually dimorphic, or whether hormonal influence on memory and cognition is more global in nature. Finally, memory has not been studied previously in M-F transsexuals in association with oestrogen treatment.

1.13. Aim of Present Research

The following research used a transsexual population to study the activating effects of administered cross-sex hormones on memory, cognition and mood. Due to the small numbers of F-M transsexuals, M-F transsexuals formed the population for the research. Therefore, the following research tests the hypothesis that M-F transsexuals taking oestrogen treatment show enhancement in memory and cognitive abilities

at which females excel and impairment in memory and cognitive abilities at which males excel. No activating hormonal influences were predicted on tasks showing no sex difference. The research also tested the hypothesis that mood would be improved by oestrogen treatment.

The following research attempts to also address some of the potentially confounding factors discussed earlier (see section 1.9.). Confounding variables in sex research include the influence of handedness, age, mood, and sexual orientation. To minimise the potential impact of mood changes associated with being put on or taken off oestrogen, mood will be measured. The third study (Chapter 4) uses a repeated measures design, so that effects of sexual orientation or handedness would be constant when on and off oestrogen. The repeated measures design also helps with influences of age, and as with mood, age will be recorded to examine whether it is having an impact on your results. In controlling for these possible influences, any change in memory, cognition or mood coinciding with cross-sex hormone treatment can be attributed to the hormone manipulation rather than to the individual differences in these other confounding variables.

Table 1: Past research on cognition in postmenopausal women

SOURCE	N	AGE	METHOD	COGNITIVE TESTS USED	TYPE AND DOSAGE OF HORMONE	FOLLOW UP	FINDINGS
Caldwell and Watson (1952).	30 aged women.	Age range = 54-88. Mean age = 75.17 years.	Mixed design. Repeated testing in 2 groups (experimental versus control)	WMS: *Mental control *Digit Span *Logical Memory *Verbal Paired Associate Learning *Visual Reproduction	First stimulated intramuscularly with 3 mg. of oestradiol benzoate per week for 6 weeks). Medication withdrawn for 1 week. This stimulation was continued for 3 weeks, following which it was withdrawn for 1 week. Then oestradiol benzoate was reduced to 2 mg. Progesterone (5 - 10 mg.) was added for 1-3 days to induce bleeding.	12 weeks (tested twice)	<u>Logical Memory</u> : In the control group, scores decreased significantly. In the experimental group, scores improved or remained the same. <u>Verbal Paired Associate Learning</u> : In the experimental group scores increased. <u>Digit Span</u> : No change in performance was seen in either group. <u>Visual Reproduction</u> : Both groups improved in performance on this task, however only the control group improved significantly. <u>WMS total score</u> : Control group scores decreased slightly (although non-significantly). The experimental group scores significantly increased from time 1 to time 2.
Ditkoff et al. (1991).	36 surgically menopausal women.	Age range = 45-60. Mean age = 53 years.	Randomised, double-blind, placebo-controlled, clinical trial. 3 groups tested twice. 2 groups taking ERT, 1 placebo group.	WAIS: *Digit Span *Digit Symbol	Premarin: either 0.625 mg. (group 1) or 1.25 mg (group 2) for 25 days each month for 3 consecutive months.	Tests were carried out before and 3 months after treatment.	There were no differences in scores on Digit Span or Digit Symbol before treatment or in association with oestrogen treatment.
Phillips and Sherwin (1992b).	19 surgically menopausal women.	48.2/4.7 years/SD.	Randomised, double-blind, placebo-controlled design. Repeated testing in 2 groups (experimental versus placebo).	WMS: *Verbal Paired Associate Learning *Visual Reproduction *Logical Memory *Digit Span	3 monthly injections of 10 mg oestradiol (E2) valerate given postoperatively. The placebo group received monthly injections of sesame oil.	Tested 1 week preoperatively (baseline) and then 2 months postoperatively (2-4 days after 3 rd monthly injection).	Scores remained the same in the HRT group for Verbal Paired Associate Learning, but decreased significantly from pre to post operatively in the placebo group. Logical Memory (immediate recall) improved in the HRT group compared to baseline scores. The placebo group showed no change for Logical Memory scores (immediate recall). No change was observed on the other tasks.

Table 1 continued

SOURCE	N	AGE	METHOD	COGNITIVE TESTS USED	TYPE AND DOSAGE OF HORMONE	FOLLOW UP	FINDINGS
Barrett-Connor and Kritz-Silverstein (1993).	800 women.	Aged 65-95 years. Mean age = 6.7 years/SD.	Between subjects. Never users, past users and current users compared.	<ul style="list-style-type: none"> *Buschke-Fuld Selective Reminding Test (Buschke and Fuld, 1974) *Visual Reproduction (WMS) *Mini Mental State Examination (MMSE) (Folstein, Folstein and McHugh, 1975) *Blessed Information-Memory 	Almost all of the oestrogen reported by women was unopposed oral oestrogen, primarily Premarin. No other hormone information was given.	Former users had used oestrogen for an average of 7.7 years, compared with current users who had used oestrogen for an average of 19.1 years	None of the cognitive tests were consistently associated with current or past use of oestrogen, duration of use or dosage.
Kimura (1995).	54 healthy postmenopausal women with usual postmenopausal complaint s (symptomatic).	Mean age = 58 years.	Mixed design Not random assignment. 21 women taking oestrogen versus 33 control women (not taking oestrogen and matched for age, education and vocabulary scores). Most of the controls had never been on HRT.	<ul style="list-style-type: none"> *Advanced Vocabulary (Kit of Factor-Referenced Cognitive Tests - KFCT) (measure of IQ) 4 functional groups of 2 tests each: <ul style="list-style-type: none"> i) Perceptual Speed *Identical picture (KFCT) *Finding As (KFCT) ii) Spatial *Card Rotations (KFCT) *Hidden Patterns (KFCT) iii) Articulatory motor *The Manual Sequence Box (Kimura, 1977; 1986) *a tongue twister iv) Verbal Fluency *Making sentences (KFCT) *Color Naming (Kimura, 1986). *Inference test (KFCT) *Verbal memory (Kramer, Delis and Daniel, 1988). 	Premarin: minimum dosage of 0.625 mg. per day for the first 25 days of the month. 5 of the 21 women also took Provera (medroxyprogesterone) on days 16-25. All women stopped hormone therapy from day 26 to the end of the month. Duration of hormone treatment was not stated.	Each woman was tested twice, about 6 weeks apart. Women on hormone therapy were tested when taking oestrogen alone (between 10 and 25 days) and when they were off all therapy.	Overall, women on therapy had better scores than those not on therapy.
Resnick et al (1997).	288 non-demented, postmenopausal women.	Subjects were aged 40 years and over. Mean age of current users = 61.8/9.1 years/SD. Mean age of never treated = 67.7/11.1 years/SD.	Mixed design. Current oestrogen users (n = 116) versus never treated (n = 172). There were some follow up data on 18 women previously tested when they were not taking ERT to be compared to their performance when later taking ERT. Controls matched for age and BVRT at initial assessment.	<ul style="list-style-type: none"> *Benton Visual Retention Test (BVRT). A measure of short-term visual memory, visual perception and constructional skills. 	Women were either taking oral/and or transdermal oestrogens. Information on dosage was not available.	Duration of treatment varied among current oestrogen users from < 6 months (n = 5) to > 20 years (n = 8), the mode duration being 1 year to < 5 years (n = 49). For the repeated testing analysis, the interval between test sessions was 6.5 years.	ERT users made significantly fewer total errors than never users on the BVRT. There was an increase in errors with age for the never treated women in comparison with a relatively stable number of errors in those taking ERT. Therefore, ERT seems to protect against age changes in the BVRT.

Table 1 continued

SOURCE	N	AGE	METHOD	COGNITIVE TESTS USED	TYPE AND DOSAGE OF HORMONE	FOLLOW UP	FINDINGS
Carlson and Sherwin (1998).	Men (n = 31); Women oestrogen users (n = 14); and Women oestrogen non-users (n = 41).	Mean age = 72.1/5.6 years/SD	Between subjects.	<p>Verbal Memory (WMS/WMS-R)</p> <ul style="list-style-type: none"> * Paragraph Recall * Verbal Paired Associate Learning * Visual Paired Associate Learning * Figural Memory <p><u>Concentration and Attention/Short Term Memory</u></p> <ul style="list-style-type: none"> * Digit Span (WMS-R) * Language Fluency/Semantic Memory * Category Retrieval (Drachman and Leavitt, 1972) 	<p>Premarin: 0.625 mg. daily (n = 9); esterified oestrogens (Neo-Estrone), equivalent dose to those on Premarin (n = 5). Mean duration = 19.14 / 19.5 years (ranging from 2 to 34 months)</p>	none	<p>Oestrogen users performed significantly better than the age-matched women oestrogen non-users on total and forward Digit Span. Both groups of women scored higher than the men on the category retrieval test.</p> <p>Scores did not differ significantly between groups for other verbal memory tests, although women receiving oestrogen had higher scores on these tests. Men excelled on Figural memory and visual memory span.</p>
Shaywitz et al (1999).	46 postmenopausal women. Community volunteers in a community setting.	Age range = 33-61 years. Mean age = 50.8/4.7 years/SD.	Randomised, double-blind, placebo-controlled, cross-over design.	<ul style="list-style-type: none"> * Verbal working memory: pronounceable nonsense words. * Non working verbal memory: Tamil letters (for non-Tamil speakers these characters are coded as complex geometric patterns). <p>Magnetic Resonance Imaging was (MRI) used to identify brain areas showing oestrogen effects and/or oestrogen interactions with task (encode, store or retrieve) and stimulus type (nonsense words or Tamil).</p>	<p>Women were treated for 2 periods of 21 days each. The first period with conjugated equine oestrogens (1.25 mg per day) and the second period with identical placebo. There were 14 days of washout between treatments.</p>	Not stated	<p>Oestrogen produced significant alterations in brain activation patterns as women performed working memory tasks.</p> <p>Increased activation was demonstrated in the inferior parietal lobule during tasks requiring temporary storage of phonologically coded verbal materials (nonsense words). Decreased activation was found in this area during storage of non-verbal tasks.</p> <p>There was no significant change in performance on these tasks. Failure to detect a change in performance coinciding with changes in brain activation may result from ceiling effects</p>

Table 1 continued

SOURCE	N	AGE	METHOD	COGNITIVE TESTS USED	TYPE AND DOSAGE OF HORMONE	FOLLOW UP	FINDINGS
Hogervorst et al (1999).	<p><u>Study 1:</u> 22 healthy menopausal women (control group = 11, HRT group = 11).</p> <p><u>Study 2:</u> 23 female HRT users = 319 female case-controls</p>	<p><u>Study 1:</u> Age range = 45-65 years. Mean age of users = 54.3 years. Mean age of controls = 55.2 years.</p> <p><u>Study 2:</u> Age range = 45-65 years. HRT users = 54.3 years and controls = 55.2 years.</p>	<p><u>Study 1:</u> Mixed design. Groups matched on age, postmenopausal complaints and social class.</p> <p><u>Study 2:</u> Between subjects</p>	<p><u>Study 1:</u></p> <ul style="list-style-type: none"> *Visual verbal learning test with distraction (Brand and Jolles, 1985). <p><u>Study 2:</u></p> <ul style="list-style-type: none"> *Verbal learning Test (VLT) (Brand and Jolles, 1985) *The Concept shifting test (CST) *The Stroop-Color-Word Test (SCWT). *Subjective complaints about memory 	<p><u>Study 1:</u> First 16 days of the month, women received 2 mg. 17-β-oestradiol, followed by 12 days with additional 2.5 or 5 mg. progestagen. Treatment lasted 1 year. Cognitive testing carried out when oestrogen and progestagen levels were elevated (day 16-28).</p> <p><u>Study 2:</u> Oestrogens, n = 9 (Premarin 0.625-1.25 mg. for 28 days; Estraderm 4-8 mg. every 24 hrs; Progynova ½ mg. for 21 days in a month; Synapause ½ mg. for 21 days in a month). Combination therapy: n = 9 (Premarin + Medrogestron (P) 0.625-1.25 mg. for 28 days + P 5mg. for days 17-28; Prempak C + Norgestrol (P) for days 28 days + P 0.15mg. for days 17-28; Estracomb TTS 4 mg. per day for 14 days, E2 10 mg. + P 30 mg. for 10 days, E2 1 mg for 14 days; Trisequens E2 2 mg. + E2 2 mg. + P 1 mg. for 10 days, E2 1 mg for 6 days; Livial - Progesterone and weak oestrogen effects 2.5 mg. per day); Other combinations, n = 5 (Premarin + 0.625-1.25 mg. for 28 days + Provera 5/10 mg. (for 28 days; Estraderm 4/8 mg. every 24 hrs. + Orgametril 5 mg for 12/15 days; Synapause-E3 2mg. for 12 days + Trisequens (P) 1 mg. for 10 days + oestradiol 1 mg. for 6 days. (See key below)</p>	<p><u>Study 1:</u> Tested at baseline, 6 and 12 months.</p> <p><u>Study 2:</u> none.</p>	<p><u>Study 1:</u> Long-term enhancements in memory at 6 and 12 months in HRT users, when compared to their baseline, but not to controls.</p> <p><u>Study 2:</u> HRT users complained more of forgetfulness. HRT users scored higher on the sensori-motor speed compound score (CST + SCWT). No between group difference in VLT scores</p>

Table 1 continued

SOURCE	N	AGE	METHOD	COGNITIVE TESTS USED	TYPE AND DOSAGE OF HORMONE	FOLLOW UP	FINDINGS
Duka et al (2000).	37 elderly subjects.	Age range = 55-75 years. Mean age = 65/4.9 years SD.	Mixed, double-blind design. Subject randomly assigned. 19 taking oestrogen versus 18 controls. Repeated testing for both groups.	<ul style="list-style-type: none"> *National Adult Reading Test (estimate of IQ) (NART-Nelson, 1985) *Berlin Tests of Associative Memory (BETAM, Based on Duka, Redemann and Voet, 1995). *Paired Associate Learning - Cambridge Neuropsychological Test Automated Battery (CANTAB) *Intradimensional/extradimensional Shift and Reversal task (CANTAB) (Owen, Roberts, Polkey, Sahakian and Robbins, 1991). *Stroop *Random Number Generation Task (Brugger, Monsch, Salmon and Butters, 1996). *Tower of London (CANTAB) (Owen, Downes, Sahakian, Polkey and Robbins, 1990) *Mental Rotations (Vandenberg and Kuse, 1978). 	A 25 cm ² patch (Progynova TS) containing 7.8 mg. oestradiol was transdermally delivered. Controls received a placebo patch.	Tested before and after 3 weeks hormone treatment.	<p>Results indicated a selective improvement in performance on learning and memory tasks.</p> <p>BETAM: A significant increase in the group receiving oestradiol was observed (delayed recall of objects)</p> <p>Paired Associate Learning: A significant increase in the group receiving oestradiol was observed (number of errors).</p> <p>Mental Rotation: Women receiving oestrogen for 3 weeks outperformed women receiving placebo.</p> <p>No significant between or within group effect on any other cognitive task were found.</p>

Table 1 continued

SOURCE	N	AGE	METHOD	COGNITIVE TESTS USED	TYPE AND DOSAGE OF HORMONE	FOLLOW UP	FINDINGS
Binder et al (2001).	52 elderly postmenopausal women.	Age range = 75-91.	Randomised, placebo-controlled.	<ul style="list-style-type: none"> *Verbal Fluency (Isaacs and Kennie, 1973) *WMS: Verbal Paired Associate Learning *Trailmaking A and B (Reiten, 1958) *Cancellation Random Letter (Weintraub and Mesulam, 1985) *Random Form Test (Weintraub and Mesulam, 1985) 	0.625 mg/day, conjugated oestrogens and tri-monthly medroxyprogesterone 5mg. per day for 13 days.	9 months	No significant group differences were found between placebo and HRT group on any of the cognitive measures, after 9 months of treatment.
Farrag (2002).	35 women. All had undergone total abdominal hysterectomy and bilateral salpingo oophorectomy for non-malignant causes. 18 control women matched on age, education, body weight and parity.	Not stated	Mixed design. Patients and controls tested at baseline, 3 and 6 months.	<ul style="list-style-type: none"> *Mini Mental State Examination (MMSE) (Folstein, Folstein and McHugh, 1975) WMS: *Digit Span *Logical Memory *Mental Control *Paired Associate Learning *Visual Reproduction 	None	None	<p>No significant differences were seen between patients and controls on age, education, age at menarche, parity, weight and on baseline of WMS and MMSE scores.</p> <p>At 3 and 6 months there were no differences in WMS and MMSE scores for the control group. For the surgery group, there was a significant decline in MMSE (especially orientation, attention and calculation).</p>

Table 1 continued

SOURCE	N	AGE	METHOD	COGNITIVE TESTS USED	TYPE AND DOSAGE OF HORMONE	FOLLOW UP	FINDINGS
Rapp et al (2003).	4381 postmenopausal women.	Aged 65 or older.	Randomised, placebo-controlled, clinical trial. Oestrogen + Progesterin (n = 2145) group versus placebo (n = 2236).	*Mini Mental State Examination (MMSE) (Folstein, Folstein and McHugh, 1975)	Conjugated equine oestrogens: 0.625 mg. per plus 2.5 mg. of medroxyprogesterone acetate, daily.	Followed up after an average of 4.2 years, comparing baseline to during therapy.	The mean rate of change in MMSE scores over time was slightly less favourable in the oestrogen plus progesterin group than the oestrogen plus placebo group over an average follow-up of 4.2 years. More women in the oestrogen plus progesterin group had a substantial clinically important decline in MMSE compared to placebo group.
Shumaker et al (2003)	4532 postmenopausal women	Aged 65 or older.	Randomised, placebo-controlled, clinical trial. Oestrogen + Progesterin (n = 2229) group versus placebo (n = 2303).	*Mini Mental State Examination (MMSE) (Folstein, Folstein and McHugh, 1975) *Consortium to Establish a Registry for Alzheimer's Disease (CERAD).	Conjugated equine oestrogens: 0.625 mg. per plus 2.5 mg. of medroxyprogesterone acetate, daily.	Followed up after an average of 4.05 years, comparing baseline to during therapy.	MMSE scores were clinically significantly lower in the oestrogen plus progesterin group than the oestrogen plus placebo group over an average follow up of 4.05 years. Incidence of dementia was also increased in the former group.
Shaywitz et al (2003)	60 postmenopausal women	Age range = 32.8 to 64.9 years.	Randomised, double-blind, placebo-controlled.	*Gray Oral Reading Test WMS: *Logical Memory *Paired Associate Learning	Premarin: 1.25 mg, daily, for 21 days.	none	The group receiving daily treatment with oestrogens showed better performance on the two verbal memory tasks and the reading task, than the placebo group.

Key

Hormone preparations

Trade name

Generic name

Oestrogens

Premarin

Estraderm

Progynova

Synopause

Delestrogen

Menest or Estratab

Combination Therapy

Premarin +

Prempak C

Estracomb TTS

Trisequens

Livial

Other combinations

Premarin (E) + Provera (P)

Estraderm (E) + Orgametril (P)

Synopause-E3 (E) + Trisequens

Conjugated oestrogens (CEE)

Oestradiol (E2)

Oestradiol (E2)

Estril (E3)

Esterified oestrogens

Oestradiol valerate (E2)

CEE + Medrogestron (P)

CEE + Norgestrol

Oestradiol + Norethisteron (P)

Oestradiol + Norethisteron (P)

Tibolon

Conjugated oestrogens (E) + Medroxyprogesteron (P)

Oestradiol (E2) + Lynestrenol (P)

Estril (E3) + Oestradiol (E2) + Norethisteron (P)

Table 2: Past research on cognition and mood during the menstrual cycle

SOURCE	N	AGE	METHOD	COGNITIVE TESTS USED	MENSTRUAL PHASE	METHOD OF DEFINING MENSTRUAL CYCLE PHASE	RESULTS
Gordon and Lee (1986).	62 men and women. Men = 32, women = 30.	Age range = 18-35 years.	Mixed design: men tested twice, one week apart. Women tested 3 times at intervals to coincide with menstrual, follicular and luteal phases of their cycle.	The Cognitive Laterality Battery (Gordon 1986) 1) Visuospatial factor *Localisation *Orientation (spatial rotation) *Touching blocks *Form completion 2) Sequential and Verbal factor *Serial sounds *Serial numbers *Word production, Letters *Word production, Categories	Women tested 3 times at intervals to coincide with menstrual, follicular and luteal phases of their cycle.	Hormone assays were collected before testing and then after each test.	<p><u>Sex differences:</u> Women were poorer than men on the visuospatial factor and verbal fluency.</p> <p>There was a negative correlation between Follicle-Stimulating Hormone (FSH) and visuospatial function (orientation test). FSH and Luteinizing Hormone (LH) correlated positively with word production (categories), but not for sequencing tasks.</p> <p>Oestrogen negatively correlated with performance on the sequential tests. Progesterone had no consistent relationship with the cognitive measures.</p> <p>There were no differences in performance between cycle phases.</p>
Hampson and Kimura (1988).	34 normal, healthy adult women.	Mean age = 24.64 years.	Repeated measures. Women tested twice, approximately 6 weeks apart.	*Rod and Frame (Oltman, 1968) *Speeded tests of manual coordination: *Finger tapping *The Manual Sequence box (Kimura, 1977) *Purdue Pegboard (Tiffin, 1968)	Tested at midluteal and menstruation phases.	Day count.	<p>Performance on the Rod and Frame was worse during the midluteal phase than at menses.</p> <p>Performance on the manual tests improved during the midluteal phase relative to menses.</p>

Table 2 continued

SOURCE	N	AGE	METHOD	COGNITIVE TESTS USED	MENSTRUAL PHASE	METHOD OF DEFINING MENSTRUAL CYCLE PHASE	RESULTS
Black and Chitwood (1990).	9 professional typists.	Age range = 24-40 years. Mean age = 33.0/5.1 years/SD	Repeated measures.	<ul style="list-style-type: none"> *10 equivalent typing tests, constructed by randomly selecting passages containing 180 words each. Passages were taken from Charles Dickens's novel 'Great Escape', (1861/2) *Anxiety Inventory (Spielberger, Gorsuch and Lushere, 1970) *Mood was assessed by a checklist devised by Plutchik (1980) 	2 tests per week were administered at intervals throughout the menstrual cycle. No specific phase was stated.	Day count	No variation in typing performance, as a function of the menstrual cycle for errors or rate of typing was found. No variation of self-reported mood with menstrual cycle phase was observed.
Hampson (1990c).	45 healthy (university students).	Age range = 19-39 years. Mean age = 23.7 years.	Repeated measures. Tested twice, 6 weeks apart.	<ul style="list-style-type: none"> Spatial ability. *Rod-and-Frame test (Oltman, 1968) *The Hidden Figures Test (Ekstrom, French, Harman and Derman, 1976) *The Space Relations subtest of the Differential Aptitude Test, Form A (Bennett, Seashore and Wesman, 1947) Perceptual Speed: <ul style="list-style-type: none"> *Number Comparisons (Ekstrom et al, 1976) *Identical Pictures Test (Ekstrom et al, 1976) *Subtraction and Multiplication (Ekstrom et al, 1976) Verbal Fluency. <ul style="list-style-type: none"> *The Oral Fluency Test (Benton, 1968) *Expressional Fluency test (Christensen and Guildford) Articulation: <ul style="list-style-type: none"> *Speeded Counting *Colour reading and naming (Uhlmann, 1962) *Syllable Repetition (Mateer and Kimura, 1977) Manual speed/coordination: <ul style="list-style-type: none"> *Purdue Pegboard (Tiffin, 1968) *Finger Tapping *The Manual Sequence Box (Kimura, 1977) Deductive reasoning <ul style="list-style-type: none"> *The Inference Test (Ekstrom et al, 1976) 	Testing was arranged to coincide with menstrual and the midluteal phases.	Day count.	There was no change in perceptual speed and verbal listening. Enhanced performance was observed on tests of articulatory and fine motor skills observed during the midluteal phase, while performance on tests of spatial ability and abstract reasoning was poor at that time, compared with performance during menses.

Table 2 continued

SOURCE	N	AGE	METHOD	COGNITIVE TESTS USED	MENSTRUAL PHASE	METHOD OF DEFINING MENSTRUAL CYCLE PHASE	RESULTS
Hampson (1990a).	50 healthy women.	Age range = 20-43 years. Mean age = 26.4 years	Repeated measures. Tested twice, 6 weeks apart.	Same battery of tests as used in Hampson (1990c) (see above) *Profile of Mood States (POMS) (Lorr and McNair, 1988)	Testing was arranged to coincide with menstrual and the late follicular (the preovulatory oestrogen surge) phases.	Day count. Hormonal assays were collected at the end of each testing session to confirm menstrual cycle phase by measuring oestrogen and progesterone and luteinizing hormone.	There was no change in perceptual speed and verbal listening. Enhanced performance was observed on tests of articulatory and fine motor skills observed during the late follicular phase, while performance on tests of spatial ability was poor at that time, compared with performance during menses. All 6 subscales of mood (Tension, Depression, Anger, Vigor, Fatigue and Confusion) showed significant variation across menstrual cycle. More positive feelings were reported during the oestrogen surge.
Hampson (1990b).	29 healthy young women (oral contraceptive users-OCs).	Age range = 20-30 years. Mean age = 22.2 years.	Between subjects. Data from the 29 women taking OCs were compared with published data (Hampson, 1990a and c) of women not taking OCs at the menstrual (n = 23) and midluteal (n = 22) phase of their cycles.	Same battery of tests as used in Hampson (1990c) (see above)	Women had been on low-dose oral contraceptives (OCs) (35mcgs. or less ethinyloestradiol for a mean of 29.7 months. OCs mimic the hormonal environment of the midluteal phase.	none	OC users performed better than menstruating women on manual speed/co-ordination, speeded articulation and perceptual speed and accuracy. Differences were not significant for the spatial composite or the Inference tests, however menstruating women did score higher on these tasks. Performance of OC users in relation to women tested in the midluteal phase was variable.

Table 2 continued

SOURCE	N	AGE	METHOD	COGNITIVE TESTS USED	MENSTRUAL PHASE	METHOD OF DEFINING MENSTRUAL CYCLE PHASE	RESULTS
Compton and Levine (1997).	24 women	Age range 19-34 years. Mean age = 24.04/4.74 years/SD.	Repeated measures	<p>3 Choice reaction time tasks.</p> <ul style="list-style-type: none"> *Lexical decision *Face decision task 1 *Face decision task 2 (Heister, Landis, Regard and Schroeder-Heister, (1989). <p>*Chimeric faces (Levy, Heller, Banich and Burton, 1983)</p> <p>*Profile of Mood States (POMS) (Lorr and McNair, 1988)</p>	Tested four times at stages of the menstrual cycle: 1) Menstrual 2) Follicular 3) Follicular (as timing of ovulation is unpredictable 4) Mid-luteal.	Cervical mucus secretions and Basal body temperature were observed daily by the participant to confirm the timing of the test session relative to the menstrual cycle.	No overall effect of cycle phase was found on any of the scores. There was no overall effect of cycle phase on mood scores, although a significant negative relationship was found between depressed mood and perceptual asymmetry on a face perception task.
Epting and Overman (1998).	47 men and women	Men: Age range 18-26 years. Mean age = 21.05 years. Women: Age range = 17-22 years. Mean age = 19.11 years.	Repeated measures. Men were tested twice, 6 weeks apart. Women tested twice at different stages of the menstrual cycle.	<ul style="list-style-type: none"> *Mental Rotations (Vandenberg and Kuse, 1978) *Rod and Frame (Oltman, 1968) *Finger tapping *Object and Location memory (Silverman and Eals, 1992) *Water Level *Purdue Pegboard 	Tested at midluteal and menstruation phases.	Ovulation detection kits used to specify cycle phase	<p>Finger tapping showed sex differences in the opposite direction predicted (in this study finger tapping favoured males). Object and Location memory showed no sex difference. All other tasks showed sex differences in the predicted direction, e.g., Performance on Mental Rotations, Rod and Frame and Water level favoured males, whereas performance on the Purdue Pegboard favoured females.</p> <p>None of the tests showed significant effects of cycle phase.</p>

Table 2 continued

SOURCE	N	AGE	METHOD	COGNITIVE TESTS USED	MENSTRUAL PHASE	METHOD OF DEFINING MENSTRUAL CYCLE PHASE	RESULTS
Maki (2002).	16 women	Age range = 18-28 years. Mean age = 20.13/3.18 years/SD.	Repeated measures	<ul style="list-style-type: none"> *Category exemplar generation (implicit memory) *Category-cued recall (explicit memory) *Fragmented Object Identification *Grooved Pegboard test (fine motor coordination) (Reitan, 1974) *Verbal Fluency *Mental Rotations (Vandenberg and Kuse, 1974) *PANAS (a 20 item list of adjectives describing positive and negative affect) (Watson, Clark and Tellegen, 1988). 	Tested at follicular, menstrual and midluteal phases	Day count. Hormonal assays were collected at the end of each testing session to confirm menstrual cycle phase by measuring oestrogen and progesterone levels.	<p>Performance on category exemplar generation (conceptual implicit memory) was better at the midluteal than the follicular phase. Performance on category-cued recall (explicit memory) did not differ across the menstrual cycle.</p> <p>At session 1, women in the follicular phase performed better on the fragmented object identification task (implicit memory) than during the midluteal phase. There was a decrease in performance on Mental Rotations and improved perceptual motor skills and Verbal Fluency in the midluteal phase.</p> <p>Oestradiol levels correlated positively with Verbal Fluency phase and negatively with Mental Rotations and perceptual motor skills, suggesting that oestrogen and not progesterone was responsible for the observed changes in cognition.</p> <p>Mood did not differ across cycle phase.</p>

Table 3: Mood and Hormone Replacement Therapy

SOURCE	N	AGE	MOOD ASSESSMENT USED	TYPE, DOSAGE AND DURATION OF HORMONE OR OTHER TREATMENT	METHOD	FINDINGS
Klaiber et al (1979).	40 severely depressed women. 23 women were receiving ERT. Of this group 15 women were premenopausal and 8 women were postmenopausal. There were 17 women receiving a placebo treatment. Of this group, 12 women were premenopausal and 5 women were postmenopausal.	ERT group: Mean/SD age of premenopausal women = 32.1/6.4 years. Mean/SD age of postmenopausal women = 48.8/5.8 years. Placebo group: Mean/SD age of premenopausal women = 31.5/8.3 years. Mean/SD age of postmenopausal women = 50.6/10.9 years.	*Hamilton Scale of Depression (HSD) (Hamilton, 1960)	5 mg. Premarin, daily for 3 months. Dosage was increased in 5 mg. steps each week if the patient failed to show improvement in depression scores. Maximum dose was arbitrarily set at 25 mg. daily. Of the 23 taking ERT, 5 women took 15 mg; 6 women took 20 mg; and 12 women took 15 mg. 2.5 mg. Provera was added on the 21 st day of oestrogen treatment and continued for 5 days. Oestrogen and progesterone were stopped to allow for menstrual flow in the premenopausal women. The placebo group had a placebo progestin.	Double-blind, between group study.	Pre-treatment scores in Hamilton scores were very similar between the oestrogen-treated and placebo groups. After 3 months, the oestrogen group's depression scores decreased. The oestrogen group progressed from a 'severely' depressed to a 'moderately' depressed condition. The placebo group's depression scores neither decreased nor improved.
Sherwin (1991).	48 healthy, perimenopausal women. Group A: n = 15 Group B: n = 10 Group C: n = 11 Group D: n = 12	Age range = 45-47 years. Group A: 49.6/5.7 years/SD Group B: 52.8/2.6 years/SD Group C: 51.7/4.1 years/SD Group D: 52.4/3.2 years/SD	*The Marital Adjustment Scale (MAS) (Locke and Wallace, 1959) *General Health Questionnaire (GHQ) (Nelson (1978) *Menopausal Index (Blatt, Wiesbader and Kupperman, 1953)	Group A: Received 0.625 mg. Premarin for 25 days, orally, of each month for 12 consecutive months and 5 mg. Provera, orally, from days 12-25 of each month. Group B: Received the same dosage and duration of Premarin as group A. A placebo was given from days 12-25 of each month. Group C: Received 1.25 mg. of Premarin for 25 days, orally, of each month for 12 consecutive months and 5 mg. Provera, orally, from days 12-25 of each month. Group D: Received the same dosage and duration of Premarin as group C. A placebo was given from days 12-25 of each month.	Mixed design. Participants were tested before treatment and then randomly assigned to 1 of 4 cyclic sequential hormone regimens (Groups A-D). They were tested 5 times during the year of treatment.	Those treated with oestrogen had an enhanced mood. Provera seemed to dampen mood in women, in a dose-dependent manner. Mood scores of participants who had received 0.625 mg. Premarin plus placebo did not differ from those that had taken 1.25 mg. Premarin plus placebo. When Provera added to 0.625 mg. of Premarin, women experienced more dysphoric mood than those given 0.625 mg. with placebo. When Provera added to 1.25 mg. of Premarin no differences in mood were found with the placebo groups.

Table 3 continued

SOURCE	N	AGE	MOOD ASSESSMENT USED	TYPE, DOSAGE AND DURATION OF HORMONE OR OTHER TREATMENT	METHOD	FINDINGS
Ditkoff et al (1991).	36 surgically menopausal women.	Age range = 45-60. Mean age = 53 years.	*Beck Depression Inventory (BDI) (Beck, 1967)	Premarin: either 0.625 mg. (group 1) or 1.25 mg (group 2) for 25 days each month for 3 consecutive months.	Randomised, double-blind, placebo-controlled, clinical trial. 3 groups tested twice. 2 groups taking ERT of differing dosages, 1 placebo group.	Both dosages of estrogen reduced depression scores compared to placebo. There were no dose-response effects.
Schneider et al (1997).	358 elderly depressed women outpatients. 72 women received ERT, 186 women did not. Women were randomly assigned to 2 groups: Group A: ERT plus fluoxetine Group B: ERT plus placebo	Aged 60 or older. Mean age = 67.9 years.	*Hamilton Scale of Depression (HSD) (Hamilton, 1960) *Geriatric Depression Scale (GDS)	Premarin (74%); oestradiol (5.6%); estropipate (5.6%); transdermal oestradiol (5.0%), intramuscular oestradiol (2.8%); ethinyloestradiol (1.4%); oestrogen/methyltestosterone (1.4%); esterified oestrogen (1.4%) and unspecified (2.8%). Those taking Premarin were taking between 0.625 and 1.25 mg., daily. 17% were taking Provera. mg., daily.	Mixed subjects. 6 week randomised, placebo-controlled, single-blind study.	No significant differences between ERT and non-ERT groups were detected on Hamilton scores at baseline. A significant interaction effect was found between ERT status and treatment. Patients taking ERT who received fluoxetine had substantially greater Hamilton score improvement than patients taking ERT who received placebo.
Klaiber et al (1997).	38 menopausal women.	Age range = 45-65 years, mean age = 53.3/4.84 years/SD	*Profile of Mood States (POMS) (Lorr and McNair, 1988) *Hamilton Scale of Depression (HSD) (Hamilton, 1960)	Phase I: all had 28 days placebo observation. Phase II: Group A administered estropipate (oestrogen), 1.5 mg. daily for 2 successive 28 day cycles. Norethindrone (progesterone), 1.0 mg. was added for the last 10 days of each cycle. Placebo for group B. Phase III: Group A crossed over to receive placebo for 2 months whilst group B received estropipate and norethindrone.	Double-blind, placebo crossover design. Randomly assigned to 2 groups: Group A, n = 21; Group B, n = 17. Phase I: all had 28 days placebo observation. Phase II: Group A administered hormone treatment Phase III: Group A crossed over to receive placebo for 2 months whilst group B received hormone treatment Each participant was seen on cycle days 10 and 15.	Women with a long duration of menopause and higher serum oestradiol levels had worse mood when receiving the combined oestrogen and progesterone than did women with short duration of menopause and lower serum oestradiol levels. When oestrogen administered alone, both groups improved in mood.

Table 3 continued

SOURCE	N	AGE	MOOD ASSESSMENT USED	TYPE, DOSAGE AND DURATION OF HORMONE OR OTHER TREATMENT	METHOD	FINDINGS
Amsterdam et al (1999).	<p>Group 1: Women on ERT with major depression (n = 40)</p> <p>Group 2: Women not on ERT with major depression (n = 132)</p> <p>Group 3: Women with major depression, taking anti-depressants (n = 396)</p> <p>Group 4: Men with major depression, taking anti-depressants (n = 262)</p>	<p>Group 1: Mean age = 52.2/5.3 years/SD</p> <p>Group 2: Mean age = 51.4/5.5 years/SD</p> <p>Group 3: Mean age = 32.7/7.0 years/SD</p> <p>Group 4: Mean age = 40.2/10.9 years/SD</p>	*Hamilton Depression Rating Scale (HSD) (Hamilton, 1960)	<p>Group 1: conjugated estrogen alone (n = 25), conjugated estrogen plus medroxyprogesterone (n = 15)</p> <p>Group 2: fluoxetine, 20 mg. daily up to 8 weeks</p> <p>Group 3: fluoxetine, 20 mg. daily up to 8 weeks</p>	<p>Phase 1: 12 weeks, open-label, fixed dose fluoxetine.</p> <p>Phase 2: 1 year double-blind, relapse prevention phase with progressive placebo substitution.</p> <p>Mood evaluations were obtained weekly for 5 weeks, then bi-weekly for 1 month, then weekly until week 12.</p>	<p>Results do not demonstrate an additional anti-depressant effect assisted by ERT, compared with fluoxetine alone. Further, ERT did not enhance fluoxetine in relapse-prevention, compared to fluoxetine maintenance alone. A slightly greater relapse rate in women on ERT was observed.</p>
Hogervorst et al (1999).	<p>Study 1: 22 healthy menopausal women (control group = 11, HRT group = 11).</p> <p>Study 2: 23 female HRT users, 319 female case-controls.</p>	<p>Study 1: Age range = 45-65 years.</p> <p>Mean age of users = 54.3 years.</p> <p>Mean age of controls = 55.2 years.</p> <p>Study 2: Age range = 45-65 years. HRT users = 54.3 years and controls = 55.2 years.</p>	<p>Study 1: *Neurovegetative complaints list (NVL) (Bohen, Twijnstra and Jolles, 1992)</p> <p>*Activation-deactivation checklist (AD-ACL) (Thayer, 1986)</p> <p>Study 2: *Symptom-Check-List 90 (subscales depression, anxiety and insomnia)</p>	<p>Study 1: First 16 days of the month, women received 2 mg. 17-β-oestradiol, followed by 12 days with additional 2.5 or 5 mg. progestagen. Treatment lasted 1 year. Cognitive testing carried out when estrogen and progestagen levels were elevated (day 16-28).</p> <p>Study 2: Estrogens, n = 9 (Premarin 0.625-1.25 mg. for 28 days; Estraderm 4-8 mg. every 24 hrs; Progynova 1/2 mg. for 21 days in a month; Synapause 1/2 mg. for 21 days in a month) Combination therapy, n = 9 (Premarin + Medrogestron (P) 0.625-1.25 mg. for 28 days + P 5mg. for days 17-28; Prempak C + Norgestrol (P) for days 28 days + P 0.15mg. for days 17-28; Estracomb TTS 4 mg. per day for 14 days, E2 10 mg. + P 30 mg. for 10 days, E2 1 mg for 14 days; Trisquens E2 2 mg. + E2 2 mg. + P 1 mg. for 10 days, E2 1 mg for 6 days; Livial - Progesterone and week oestrogen effects 2.5 mg. per day); Other combinations, n = 5 (Premarin + 0.625-1.25 mg. for 28 days + Provera 5/10 mg. (for 28 days; Estraderm 4/8 mg. every 24 hrs. + Orgametril 5 mg for 12/15 days; Synapause-E3 2mg. for 12 days + Trisquens (P) 1 mg. for 10 days + oestradiol 1 mg. for 6 days.</p>	<p>Study 1: Tested at baseline, 6 and 12 months.</p> <p>Participants were always tested during the estrogen-progestagen phase. In this study participants were aware of the purpose of the study.</p> <p>Study 2: no follow up. In this study participants were unaware of the purpose of the study</p>	<p>Study 1: Women in the HRT group reported feeling more vigorous, activated and less stressed at 6 and 12 months (AD-ACL scores). HRT users had significantly lower scores on the emotional vulnerability subscale as compared with non-users after 12 months (NVL).</p> <p>Study 2: HRT users had higher anxiety and depression than non-users.</p> <p>Conclusions: Any mood enhancements may be due to expectancy effects of patients</p>

Table 3 continued

SOURCE	N	AGE	MOOD ASSESSMENT USED	TYPE, DOSAGE AND DURATION OF HORMONE OR OTHER TREATMENT	METHOD	FINDINGS
Barrett-Connor et al (1999).	699 non-estrogen using, community-dwelling postmenopausal women.	Age range = 50-90 years. Mean age = 74 years.	*Beck Depression Inventory (BDI) (Beck, 1967)	none	All women had plasma obtained for steroid hormone assays directly after mood assessment. Levels of total and bioavailable (non-SHBG-bound) oestradiol and testosterone, estrone, androstenedione, cortisol, dehydroepiandrosterone, and DHEA and its sulfate were measured.	Only DHEA scores showed a highly significant inverse association with BDI scores. A subgroup of 31 women with clinically defined depression had lower DHEAS levels compared with 93 age-matched non-depressed.
Boyle and Murrin (2001).	70 perimenopausal women: 35 women taking HRT versus 35 women not taking HRT.	Age range = 45-54 years. Mean age = 51.9/4.6 years/SD	*Profile of Mood States (POMS) (Lorr and McNair, 1988) *Eysenck Personality Questionnaire (EPQ) (Eysenck and Eysenck, 1975) *Menstrual Distress Questionnaire (MDQ) (Moos, 1986) *General Health Questionnaire (GHQ-GHQ 28 version) (Goldberg and Williams, 1985)	Differing dosages and types of hormone was not specified. 74.3% of women preferred HRT via tablets; 22.8% of women used HRT via patches; and 2.9% of women received HRT via implants.	Between subjects.	The women receiving HRT reported significantly lower scores on anxiety, insomnia and somatic symptoms, than did the comparable group not receiving HRT. All women prior to the study had experienced physical symptoms or psychological mood changes associated with the menopause.

Table 4: Men and Hormone Replacement Therapy

SOURCE	N	AGE	COGNITIVE AND MOOD ASSESSMENTS USED.	TYPE, DOSAGE AND DURATION OF HORMONE	FOLLOW UP	FINDINGS
Van Goozen et al (1995).	15 Male-to-Female (M-F) transsexuals. 20 male and 20 female controls.	Age range = 20-45 years. Mean age = 32.4 years.	*Card Rotation test (2 dimensional) (Ekstrom, French and Harman, 1976) *Verbal Reasoning test (Luteijn and Van der Ploeg, 1983) *Verbal Fluency (word production categories test) (Gordon, Corbin and Lee, 1986) *Verbal Fluency (sentence production) (Gordon, Corbin and Lee, 1986)	Anti-androgens (Androcur, 50 mg., twice a day) and oestrogens (ethinyloestradiol, 50 mcg. twice a day), administered orally for 3 months.	M-Fs were tested before commencing hormone treatment and then after 3 months of hormone treatment. Controls also tested twice at these time intervals.	Females were better at Verbal Fluency, but no sex difference was seen on the visual spatial test. The control group were more intelligent (Verbal Reasoning) and performed better on Verbal Fluency than M-F transsexuals. The control group improved on Rotated figures at the 2 nd test, whereas M-Fs scored worse. At 2 nd test M-Fs were better at word Verbal Fluency (S) but slightly worse on Verbal Fluency (W). Spatial ability decreased at 2 nd test. There was no difference on Verbal Reasoning. <u>Conclusions:</u> Cross-sex hormones directly and quickly affect gender-specific cognitive behaviours.
Kay et al (1995).	5 aggressive demented male patients.	Patient 1: 75 years old. Patients 2, 3, 4 and 5: ages not reported.	Behavioural observations of aggression.	Transdermal oestradiol patch. This delivers 0.05 mg or 0.10 mg. of oestrogen per day, for variable durations.	Daily/weekly monitoring of aggressive behaviour.	Patient 1: After commencing hormone treatment, the number of sexual assaults decreased from 19 in 10 days to 3 during the following week and none thereafter. Patients 2: After introducing treatment, total number of violent and aggressive episodes reduced by two thirds. Patient 3: Initially this patient appeared to respond to oestradiol, but by the 5 th week aggressive behaviour returned. Later hormone treatment was tried again. In combination with other medication, aggressive behaviour was substantially reduced. Patient 4: A good response in terms of reduced aggressive behaviour was seen in 3 weeks of hormone treatment. Patient 5: Improvement in behaviour was seen in behaviour over 11 weeks of hormone treatment. Behaviours returned when oestrogen treatment discontinued and diminished when oestrogen treatment was reintroduced.

Table 4 continued

SOURCE	N	AGE	COGNITIVE TESTS USED	TYPE, DOSAGE AND DURATION OF HORMONE	FOLLOW UP	FINDINGS
Miles et al (1998).	59 M-F transsexuals. 29 transsexuals were currently undergoing hormone treatment. 30 transsexuals were awaiting hormone treatment.	Patients on hormone treatment (mean age = 36.7/9.4 years/SD). Patients awaiting treatment (mean age = 33.1/10.7 years/SD).	Memory: <ul style="list-style-type: none"> *Verbal Paired Associate Learning - Wechsler Memory Scale (WMS) *Digit Span (WMS) *3 dimensional Mental Rotations (Vandenbergh and Kuse, 1987) *Controlled Associations (Ekstrom, French and Harman, 1976) *Vocabulary (Thurstone, 1963) *Profile Of Mood States (POMS) - (Lorr and McNair, 1988). 	27 patients were treated with Premarin (conjugated equine oestrogens) and 2 with ethinyloestradiol (a synthetic oestrogen). Some patients on Premarin were also receiving Provera (medroxyprogesterone acetate, a derivative of progesterone) (n = 3) or Androcur (cyproterone acetate, an anti-androgen) (n = 5). For patients receiving Premarin, dosages ranged from 2.5 to 7.5 mgs (milligrams), daily. Dosage of Provera was 5 mgs, daily and those patients taking ethinyloestradiol received 50 mcgs (micrograms), daily. Duration of hormone treatment varied from patient to patient (3-72 months).	none	Patients taking hormone treatment were better at Verbal Paired Associate Learning than patients not taking hormone treatment. There was no difference on any other cognitive or mood measure. Duration and dosage was not associated with any of the mood or cognitive measures. There was also no difference between those treated with different types of hormones on any of the memory, cognitive or mood measures.
Wagner, Rabkin and Rabkin, 1998).	66 HIV+ men with clinical hypogonadism (low libido plus at least one of the associated symptoms of depressed mood, fatigue, and weight loss).	Mean age = 40/8 years/SD.	<ul style="list-style-type: none"> *Chalder Fatigue Scale (Chalder, Berelowitz, Pawlikowski et al, 1993) *Structured Clinical Interview (Spitzer, Williams and Gibbon, 1995) *Hamilton Rating Scale for Depression (Hamilton, 1967) *Brief Symptom Inventory (Derogatis and Melisaratos, 1983) *Endicott Quality of Life Enjoyment and Satisfaction Questionnaire (Endicott, Nee and Harrison, 1993) *Clinical global impressions 	12 weeks of biweekly intramuscular injections of Testosterone cypionate. Starting dose was 200 mg, increasing at week 2 to 400 mg. biweekly.	12 weeks open trial of testosterone	4 of every 5 men who had low energy at baseline reported significant improvement. Most with clinical fatigue responded well to treatment. Whether testosterone therapy improved depressed mood directly is not known, because energy improvements was always accompanied with mood improvement. Life satisfaction and enjoyment improved when fatigue was alleviated following treatment. Results may be indicative of therapeutic approaches to older men once their testosterone levels decline.

Table 4 continued

SOURCE	N	AGE	COGNITIVE TESTS USED	TYPE, DOSAGE AND DURATION OF HORMONE	FOLLOW UP	FINDINGS
Slabbekoorn et al (1999).	20 M-F transsexuals.	Age range = 19-45. Mean age = 29.1/8.0 years/SD	<ul style="list-style-type: none"> *Verbal Reasoning test (Luteijn and Van der Ploeg, 1983) *2 dimensional Rotated Figures (Ekstrom, French and Harman, 1976) *3 dimensional Rotated Figures (Vandenberg and Kuse, 1978) *Hidden Figures (Ekstrom, French and Harman, 1976) *Verbal Fluency (Word production categories test) (Gordon, Corbin and Lee, 1986) *Verbal Fluency (Sentence production) (Gordon, Corbin and Lee, 1986) *Fine motor movement (adapted from Tiffin, 1968) *Test D2 (perceptual speed) (Brickenkamp, 1981) 	Anti-androgens (Androcur, 50 mg., twice a day) and oestrogens (ethinyloestradiol, 50 mcg., twice a day), administered orally.	Tested before hormone treatment began and then 3 months (short-term) and 10 months (long-term) later. A subgroup was tested when withdrawn from hormone therapy for 5 weeks prior to sex re-assignment surgery.	Hormone treatment prevented a learning effect for M-F transsexuals in spatial ability. Their spatial ability did not decline after 3 or 10 months when compared to pre-treatment scores. There was also no activating effect of hormone treatment on Verbal Fluency, fine motor movement or perceptual speed. No long-term effects were seen on any of the cognitive tasks. Further, after 5 weeks withdrawal of treatment no change was seen in cognitive performance. Oestrogen had no declining effect on spatial ability or an enhancing effect on Verbal Fluency.
Van Goozen et al (2002).	22 M-F homosexual transsexuals (sexual orientation towards men) 20 male and 23 female controls	<ul style="list-style-type: none"> M-Fs: Mean age = 31.4/10.8 years/SD Males: Mean age = 30.8/11.2 years/SD Females: Mean age = 30.6/9.6 years/SD 	<ul style="list-style-type: none"> *Verbal Reasoning test (Luteijn and Van der Ploeg, 1983) *Line Orientation test (Benton, Varney and Spreen, 1994) *2 dimensional Rotated Figures (Ekstrom, French and Harman, 1976) *3 dimensional Rotated Figures (Vandenberg and Kuse, 1978) *3 dimensional Rotated Figures: Same-Different (Shepard and Metzler, 1971) *Targeted throwing (spatio-motor task) (adapted from Hall and Kimura, 1995) 	Anti-androgens (Androcur, 50 mg., twice a day) and oestrogens (ethinyloestradiol, 50 mcg., twice a day).	Subjects tested twice, 1 week prior to hormone treatment and then a second time after 14 weeks. Controls were tested at the same intervals. ½ the females were tested after start of menses and the remaining, 7-10 days prior to menses.	There was no difference between groups on Verbal Reasoning. Sex differences were seen on all 5 spatial tasks. Males were better than females, although only marginally significant for Rotated Figures (2 dimensional). Mean scores of M-Fs were situated between female controls and male controls for all tasks, suggesting an organising effect. Sex differences were seen on all 5 spatial tasks. Scores were better at time 2 (except for Line Orientation and Throwing.)

CHAPTER 2: THE ASSOCIATION BETWEEN OESTROGEN, MEMORY AND COGNITION IN A MALE-TO-FEMALE TRANSSEXUAL POPULATION

Ω Data for this study was collected for my BSc (Hons) Psychology, third year research project. Work was carried out on the data set and interpretation thereafter for publication (see Appendix 1).

2.1. CHAPTER SUMMARY

In the present study Male-to Female (M-F) transsexuals undergoing oestrogen treatment for sex re-assignment (n = 29) scored higher on verbal Paired Associate Learning (PAL) compared to a similar transsexual control group, awaiting oestrogen treatment (n = 30) ($p < .05$). No differences between groups receiving and not receiving oestrogen were detected on a control memory task (Digit Span) or on other cognitive tasks including Mental Rotations and Controlled Associations. There were no group differences in age. Group differences in mood or in general intellectual ability also did not explain the findings. Results suggest a specific influence of oestrogen in men on verbal memory tasks, similar to that seen in prior studies of women. They are discussed in terms of differential

processing demands of the two memory tasks and possible differences between oestrogenic influences on Mental Rotations and Controlled Associations in men versus women.

2.2. INTRODUCTION

Chapter 1 outlines research demonstrating that oestrogen can influence behaviour in animals and humans. Further, oestrogen may have an effect on specific aspects of memory. For example, postmenopausal women taking Oestrogen Replacement Therapy (ERT) score higher on PAL tasks compared to their placebo controls.

In other species gonadal hormones, including oestrogen, influence behaviours that show sex differences, but not those that do not show sex differences (Collaer and Hines, 1995). Therefore, it may be useful to consider whether the effects of oestrogen on memory and cognition are limited to those memory and cognitive tasks that show sex differences.

To investigate this possibility, the present study looked at memory and cognitive tasks that show a sex difference and those that do not. The study focused on M-F transsexuals who are given oestrogens for psychiatric reasons. M-F transsexuals offer one of the few ethical opportunities for studying the effect of oestrogens on human males. We hypothesised that M-F transsexuals on oestrogen treatment would score higher on tasks at which females excel and lower on tasks at which males excel, than those transsexuals awaiting oestrogen treatment. For tasks showing no sex difference, we hypothesised that scores for the two groups would be similar. This pattern of difference was predicted on the basis of reports associating high oestrogen levels during the menstrual cycle with impairment on tasks at which males typically excel and enhancement on tasks at which females typically excel (Hampson and Kimura, 1988) and on previous findings that M-F transsexuals receiving cross-sex hormones show impairment on visual-spatial tasks favouring men and enhancement on Verbal Fluency, a task favouring women (Van Goozen, Cohen-Kettenis, Gooren, Frijda and Van de Poll, 1995).

2.3. METHOD

2.3.1. Participants

Fifty-nine genetic males desiring sex re-assignment as females and diagnosed as having Gender Identity Disorder, as defined in DSM IV (Diagnostic and Statistical Manual of Mental Disorders, 4th Ed.) were tested. Twenty-nine were currently undergoing oestrogen treatment (mean age = 36.7 years / SD = 9.4) and thirty were awaiting such treatment (mean age = 33.1 years / SD = 10.7). Median education level for those awaiting treatment was O'level (ranging from pre-O'level / G.C.S.E to Bachelors Degree). For those taking oestrogen, median level of education was A'level (ranging from pre-O'level to some post-Bachelors training). Data on ethnicity and socio-economic status of participants was not collected so could not be incorporated into this analysis. All patients were recruited through the Gender Identity Clinic, Charing Cross Hospital, London, England. This clinic is the national centre for sex re-assignment. Patients came from all regions of Great Britain.

2.3.2. Hormone treatment

The dosage and form of hormone treatment varied somewhat from patient to patient. Twenty-seven patients were treated with Premarin ⁷(conjugated equine oestrogens) and two with ethinyloestradiol (a synthetic oestrogen). Some patients on Premarin were also receiving Provera (medroxyprogesterone acetate, a derivative of progesterone) (n = 3) or Androcur (cyproterone acetate, an anti-androgen) (n = 5). For patients receiving Premarin, dosages ranged from 2.5 to 7.5 mgs (milligrams), daily. Dosage of Provera was 5 mgs, daily and those patients taking ethinyloestradiol received 50 mcgs (micrograms), daily. See Table 5 for dosage, duration and type of hormone for each patient. Those taking cyproterone acetate received 50 to 100 mgs, daily. Treatment form and dosage varied because each patient's physician prescribed hormones in light of each patient's presenting clinical picture and history, as well as their physical response to hormone treatment.

⁷ Constituents of Premarin: estrone sulphate (48%); equilin (26%); 17 alpha-dihydroequilin (17%); 17 alpha-oestradiol (3%); equilenin, 17 alpha-dihydroequilenin, 17 beta-dihydroequilin, 17 beta-dihydroequilenin (6%); 17 beta-oestradiol (< 1%). Both Premarin and ethinyloestradiol are more biologically potent than naturally occurring oestradiol. Regarding the relative potencies of conjugated oestrogens (e.g., Premarin) and ethinyloestradiol, in a summary by Whitehead and Godfree, (1992), they report a study that used four different parameters to assess relative oestrogen potencies. Piperazine estrone sulphate (a natural oestrogen) was ascribed a relative potency of 1. Conjugated oestrogens were 1.4 times more potent at suppressing plasma follicle stimulating hormone. Ethinyloestradiol was 80-200 times more potent for the same parameter. 50 mcg of ethinyloestradiol equates approximately to 5 mg of Premarin (Goodman and Gilman, 1985). Furthermore, in a study assessing M-F transsexuals, a dose of 50 mcg ethinyloestradiol appeared to have a similar effect to 5 mg conjugated oestrogens, in terms of breast hemicircumference (Meyer, Finkelstein, Stuart, Webb, Smith and Payer, 1981).

Table 5: Dosage, duration and type of hormone treatment for each transsexual patient.

Patient	Type of hormone	Dosage	Duration (in months)
1	Premarin	2.5	4
2	Premarin	2.5	4
3	Premarin	2.5	4
4	Premarin	2.5	5
5	Premarin	2.5	5
6	Premarin	2.5	6
7	Premarin	5.0	6
8	Premarin	5.0	12
9	Premarin	5.0	15
10	Premarin	5.0	18
11	Premarin	5.0	24
12	Premarin	5.0	24
13	Premarin	5.0	30
14	Premarin	5.0	37
15	Premarin	5.0	40
16	Premarin	5.0	42
17	Premarin	5.0	45
18	Premarin	7.5	61
19	Premarin	7.5	72
20	Premarin and Provera	2.5 / 5.0	36
21	Premarin and Provera	2.5 / 5.0	60
22	Premarin and Provera	2.5 / 5.0	60
23	Premarin and Androcur	2.5 / 100	24
24	Premarin and Androcur	2.5 / 100	3
25	Premarin and Androcur	5.0 / 50	10
26	Premarin and Androcur	7.5 / 5.0	12
27	Premarin and Androcur	7.5 / 50	36
28	ethinyloestradiol	50	36
29	ethinyloestradiol	50	40

Note. Measures of: Premarin, Provera and Androcur - in milligrams. ethinyloestradiol - in micrograms

2.3.3. Procedure

Prior to testing, written informed consent was obtained from each participant via a form approved by the Charing Cross Hospital Ethical Committee. Patients were tested individually. The main focus of the study was on memory. Due to time constraints, some subjects could not complete the full battery. In these cases, the number of patients completing cognitive tests, other than memory measures, was reduced.

2.3.4. Measures

1. Wechsler Memory Scale (WMS) - Wechsler (1945); Stone, Girdner, Albrecht (1946); as modified by Russell (1975).

Digit Span and PAL sub-tests were administered. For the Digit Span sub-test, participants listen to a series of number sequences, and are asked to repeat the numbers back in the same order or in a backwards order. The number of digits in the sequence increase and two trials are given for each sequence length. The score obtained represents the longest sequence the participant is able to repeat correctly. This task does not show a sex difference (Blum et al, 1972). For the PAL, a list of ten word pairs is read to participants (six easy-associated pairs and four hard-associated pairs).

They then are asked to supply the second word of the pair immediately after the first has been given. One point is given for a correctly recalled easy pair and two points for a correctly recalled hard pair. Three learning trials are given consecutively (immediate recall) followed by a final trial after half an hour delay (delayed recall). Each trial is scored separately as a composite of the easy and hard pairs. This task shows a sex difference favouring females (Iverson, 1977).

2. The Profile Of Mood States (POMS) - (Lorr and McNair- 1988). The

POMS was used to assess if mood at the time of testing was a confounding influence on memory or other cognitive scores. This instrument yields scores for the following bi-polar constructs: Anxious/Composed; Agreeable/Hostile; Elated/Depressed; Confident/Unsure; Energetic/Tired; Clearheaded/Confused. Scores were obtained for each participant for each construct. Given that the scales are bi-polar, each scale score is the sum of positive item scores minus the negative item scores.

Other Cognitive Tasks

3. Mental Rotations - (Vandenberg and Kuse, 1987). Participants are required to compare four rotated figures to a target figure and decide which two of the four figures are the same as the target figure. There are twenty items to complete within a ten minute time limit. One point is given when both figures in an item are correct. This and similar tasks show a sex difference favouring males (Voyer, Voyer and Bryden, 1995).

4. Controlled Associations - (Ekstrom, French and Harman, 1976). Participants are given four commonly used words and are asked to generate as many synonyms as possible. Participants have six minutes to complete the task. The number of words given is their score. This and similar tasks show a sex difference favouring females (Hines, 1990; Halpern, 1996).

5. Vocabulary - (Thurstone, 1963). Participants are presented with target words and asked to select the one of four other words most similar in meaning to the target word. Participants have six minutes to complete the task. Their score is the number of correct responses. This and similar measures of vocabulary do not show a sex difference (Hyde and Linn, 1988).

6. Demographic information. A questionnaire was administered at the close of the test session to obtain background information about the patient, including age, sex, educational history and duration and dosage of treatment with oestrogen and other hormones. Hormone treatment information was also verified by reference to medical records.

2.4. RESULTS

Participant characteristics

An initial analysis examined correlations of age and mood variables with memory and cognitive scores. Age did not correlate significantly with performance on any of these measures ($r = .01$ to $-.24$, all ns.). Furthermore, no significant age difference was found between the two groups ($t(54) = -1.32$, $p > .05$). The two groups also did not differ on any of the mood measures at the conventional significance level of $p = .05$: Anxious / Composed ($F(1,58) = 1.23$, $p > .05$); Agreeable / Hostile ($F(1,58) = .603$, $p > .05$); Elated / Depressed ($F(1,58) = 2.69$, $p > .05$); Confident / Unsure ($F(1,58) = .954$, $p > .05$); Energetic / Tired ($F(1,58) = .68$, $p > .05$); Clearheaded / Confused ($F(1,58) = 1.15$, $p > .05$). Table 6 gives descriptives for these variables. However, because of suggestions that mood is improved by oestrogen therapy, we were also interested that for all six moods the direction of group differences was such that those on oestrogen had more positive mood than those not on oestrogen. Due to this we examined correlations between mood measures and all memory and cognitive scores. Of the 54 possible relationships none was significant ($p < .05$).

Table 6: Descriptives for the mood variables

Mood	Oestrogen	Control
Composed / Anxious	23.72 / 8.34	21.27 / 8.68
Agreeable / Hostile	28.37 / 6.19	27.10 / 6.46
Elated / Depressed	25.69 / 7.21	22.30 / 8.56
Confident / Unsure	22.52 / 7.67	20.50 / 8.17
Energetic / Tired	22.97 / 7.51	21.13 / 9.44
Clearheaded / Confused	26.51 / 8.28	24.13 / 8.83

Note: Values expressed as Means / SDs.

Possible differences in educational background between the two groups were also examined. The groups differed significantly ($U = 175, p < .01$), such that those taking oestrogen were educated to a higher level than those not taking oestrogen. Education did not correlate significantly with any of the PAL trials ($r = .05$ to $.23, p > .05$), Mental Rotations ($r = .22, p > .05$), Digits Forwards ($r = .17, p > .05$) or Digits Backwards ($r = .23, p > .05$), but did correlate with Controlled Associations ($r = .48, p < .01$) and Vocabulary ($r = .51, p < .001$).

Cognitive measures

Data for cognitive and memory measures are in Table 7. Three separate ANOVAs showed no significant group differences for Mental Rotations, Controlled Associations or Vocabulary scores, suggesting that transsexual patients on and off oestrogen performed similarly on these tasks. Table 7 illustrates this.

Table 7: Performance on cognitive tasks and on Digit Span for transsexual patients treated with oestrogen (Oestrogen) versus those not treated with oestrogen (Control).

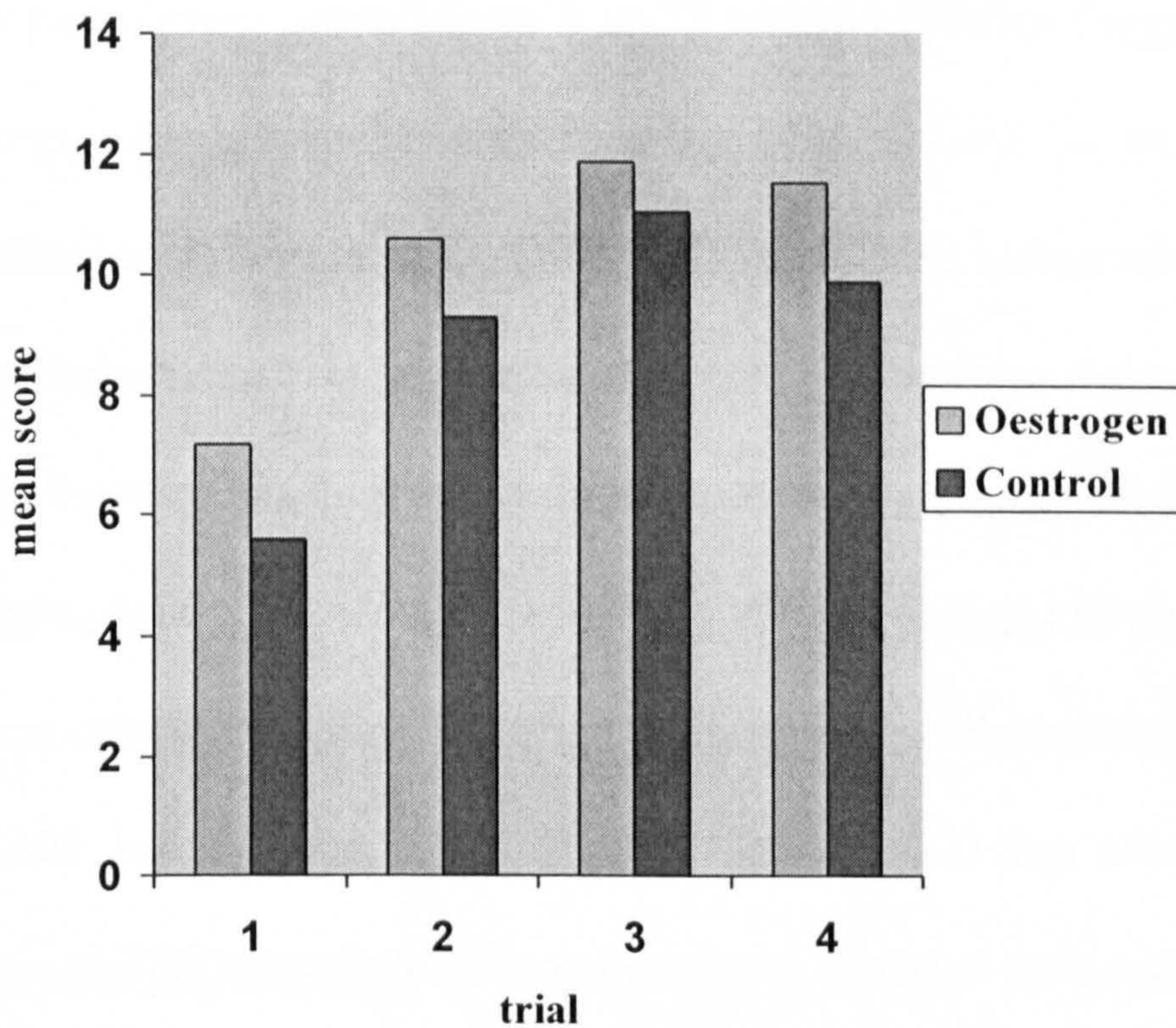
	Oestrogen		Control		
	Mean / SD	n	Mean / SD	n	d
Mental Rotations	9.71 / 5.68	21	8.29 / 4.03	24	.29
Controlled Associations	14.42 / 8.60	24	14.68 / 6.62	22	.03
Vocabulary	27.63 / 12.50	29	24.79 / 11.33	30	.24
Digits Forwards	7.00 / 1.19	29	6.93 / 1.42	30	.06
Digits Backwards	5.32 / 1.42	29	5.23 / 1.50	30	.06
PAL trial 1	7.17 / 2.66	29	5.60 / 2.90	30	.56
PAL trial 2	10.59 / 3.04	29	9.30 / 2.47	30	.47
PAL trial 3	11.86 / 2.80	29	11.03 / 2.40	30	.32
PAL trial 4	11.52 / 2.97	29	9.87 / 3.00	30	.55

Note. Cohen's d (1969) was used to calculate effect size (d).

Verbal Memory measures

Data for PAL are illustrated in Figure 2.

Figure 2: PAL Scores



A 2 (group) x 4 (trial) ANOVA produced a main effect of group ($F(1, 57) = 4.83, p = .03$), such that the oestrogen-treated group performed better overall than the control group. There was also a significant effect of trial irrespective of group ($F(3, 171) = 97.27, p < .001$). This was expected due to the repetitive nature of this learning task. Although there was no

significant interaction effect, group differences on individual trials were also examined. Post hoc comparisons revealed significant differences on trials 1 ($p = .02$) and 4 ($p = .004$), suggesting that oestrogen treatment was associated with improvement in both immediate and delayed recall.

Digit Span Scores

No main effect for group was found ($F(1, 56) = .09, p = .77$), indicating that transsexual patients receiving oestrogen treatment performed similarly on this task to those not receiving oestrogen treatment. There was a main effect of condition ($F(1, 56) = 82.55, p < .0001$), showing that both groups found the forwards condition easier than the backwards condition, as is usually true on this task (Blum et al, 1972; Caldwell and Watson, 1952). There was no interaction between group and condition. See Table 7.

Duration of Treatment

We examined the possibility that the relationship between oestrogen treatment and memory, as well as between oestrogen treatment and cognitive scores, varied with duration of treatment. Duration of treatment for participants ranged from 3 to 72 months. Within the oestrogen-treated group, correlations between duration of treatment, in months, and PAL performance were non-significant ($r = -.19, -.18, -.11, \text{ and } -.06$, for trials 1 to 4, in order, all ns.). Correlations between duration of treatment and other cognitive and memory measures were also non-significant ($r = -.06$, for Digits Forward; $r = .28$, for Digits Backwards; $r = -.04$, for Mental Rotations, $r = .15$, for Controlled Associations, and $r = .26$, for Vocabulary).

Dosage of Treatment

We examined whether dosage of oestrogen correlated with memory and cognitive scores. As only small samples were taking ethinyloestradiol; Premarin and Provera; and Premarin and cyproterone acetate, only those taking Premarin exclusively were included in this analysis ($n = 19$). All correlations between dosage and memory and cognitive scores were non-significant ($r = .10, -.01, -.34, -.18$, for trials 1 to 4, of the PAL in order, all

ns.; $r = .09$, for Digits Forwards; $r = .35$, for Digits Backwards; $r = -.04$, for Mental Rotations; $r = .11$, for Controlled Associations and $r = .33$, for Vocabulary).

Treatment with Different Hormone Combinations

As 5 patients were taking an anti-androgen in addition to Premarin, we examined whether this sub-group differed on memory and cognitive scores from those taking Premarin exclusively ($n = 19$). No significant difference was found between the sub-groups on any of the tasks (PAL ($F(1, 22) = 1.10$, $p > .05$); Digit Span ($F(1, 22) = 1.58$, $p > .05$); Mental Rotations ($t(15) = -1.57$, $p > .05$); Controlled Associations ($t(17) = -.23$, $p > .05$); Vocabulary ($t(17) = -.20$, $p > .05$)).

We also examined whether differences between individuals in the type of oestrogen taken could be distorting results. To address this, we compared the nineteen patients on Premarin only to the untreated group. Results were similar to those for the full sample. Although no longer statistically significant for the PAL trials, perhaps because sample size was reduced, effect sizes remained roughly the same for differences between patients on and off hormones (Cohen's d value was calculated by dividing the

difference between the two group means by the pooled standard deviation). No significant differences were seen between the Premarin only group and the untreated patients on Digit Span or on the three cognitive measures. Similar effect sizes were obtained for these variables as well (see Tables 4 and 5).

Table 8: Performance on cognitive tasks for transsexual patients treated with Premarin only (Oestrogen) versus those not treated with oestrogen (Control).

	Premarin only subjects				
	Oestrogen		Control		
	Mean / SD	n	Mean / SD	n	d
Mental Rotations	9.27 / 6.71	11	8.29 / 4.03	24	.24
Controlled Associations	14.71 / 8.53	14	14.68 / 6.62	22	.00
Vocabulary	28.48 / 11.27	19	24.78 / 11.33	30	.33

Note. Values expressed as means / standard deviations (SD), with sample size (n) and effect size (d).

Table 9: Performance on memory measures for transsexual patients treated with Premarin only (Oestrogen) versus those not treated with oestrogen (Control).

	Premarin only subjects				
	Oestrogen		Control		d
	Mean / SD	n	Mean / SD	n	
PAL trial 1	7.16 / 3.08	19	5.60 / 2.90	30	.52
PAL trial 2	10.58 / 3.13	19	9.30 / 2.47	30	.46
PAL trial 3	11.63 / 2.99	19	11.03 / 2.40	30	.22
PAL trial 4	11.32 / 3.00	19	9.86 / 3.02	30	.48
Digits Forwards	7.05 / 1.18	19	6.93 / 1.33	30	.01
Digits Backwards	5.16 / 1.43	19	5.20 / 1.50	30	.10

Note. Values expressed as means / standard deviations (SD), with sample size (n) and effect size (d).

Analyses of Covariance

Patients treated with oestrogen were more educated than patients awaiting treatment. To examine the possibility that differences in education or similar factors, such as general intellectual ability, were distorting our results, we conducted several analyses of covariance. The main criterion for a covariate analysis is a 'substantial linear correlation with the

dependent variable' (Keppel, 1991). Education level did not correlate with any of the PAL trials or with either Digits Forward or Digits Backward (all $p > .10$) but did correlate with scores on Vocabulary ($p < .05$). Also, correlations with Mental Rotations and Controlled Associations approached significance (both $p < .10$). For this reason we re-analysed data for these three dependent variables using education as a covariate. There were no significant differences between patients on versus off oestrogen treatment (Vocabulary, $F(1, 58) = .44, p = .51$); Controlled Associations, $F(1, 45) = 2.44, p = .13$); Mental Rotations, $F(1, 44) = .02, p = .90$)).

There were no group differences in Vocabulary scores. However, Vocabulary correlated significantly with performance on trials 1, 2 and 4 of the PAL task. Coupled with the group difference in education, this raised the concern that differences between the groups in general intellectual ability might explain differences in PAL. To address this, we re-analysed PAL data using Vocabulary score as a covariate. Results resembled those obtained in the initial analysis. There was a main effect of group ($F(1, 56) = 4.06, p = .05$) and post hoc comparisons revealed significant group differences on trials 1 ($p = .01$) and 4 ($p = .007$). Vocabulary scores also correlated significantly with Controlled Associations ($r = .52, p = .01$) and Mental Rotations ($r = .32, p = .03$), therefore, ANCOVAs using

Vocabulary as a covariate were conducted for these data as well. Results were similar to those produced by the initial analyses of data on Controlled Associations and Mental Rotations and for those using education as a covariate (Controlled Associations, $F(1, 45) = .53, p = .47$); Mental Rotations, $F(1, 44) = .59, p = .45$).

2.5. DISCUSSION

A significant difference between groups on PAL scores was detected such that M-F transsexuals on oestrogen scored significantly higher than those not on oestrogen. No group difference in Digit Span scores was found, suggesting that oestrogen may have a selective effect on a memory function that shows a sex difference. Age did not differ significantly between groups, and along with the absence of differences in Digit Span scores and other cognitive measures, makes it unlikely that generalised differences between the groups on and off oestrogen account for their differences in PAL. The group taking oestrogen was more highly educated than the group not taking oestrogen, and there was some evidence of an improvement in their mood. However, these variables did not correlate significantly with any trial of the PAL and so cannot account for the higher scores obtained by the oestrogen-treated group. In addition, although Vocabulary scores did

correlate significantly with PAL performance, analysis using Vocabulary as a covariate also indicated that patients on hormones showed enhanced PAL performance.

These findings are consistent with our hypothesis that oestrogen influences a memory test that shows a sex difference (i.e., PAL (DesRosiers and Ivison, 1988; Ivison, 1977; Mann, Sasanuma, Sakuma, and Masaki, 1990)) and has no effect on a memory test showing no sex difference (i.e. Digit Span (Blum, et al, 1972; Chavez, Trautt, Brandon, and Steyart, 1983; Makarec and Persinger, 1993; 1995)). However, we used only one test that shows a sex difference and one test that does not. Additional research, using a wider range of tests, would provide a more stringent test of the hypothesis. A female advantage has been shown on other associative memory tasks (Birenbaum, Kelly and Levi-Keren, 1994; Bleecker, 1988; Hedges and Nowell, 1995), and future research might examine whether these are influenced by oestrogen. Past research on the menstrual cycle (Phillips and Sherwin, 1992a) and postmenopausal women (Caldwell and Watson, 1952; Phillips and Sherwin, 1992b) did not conceive that the tasks influenced by oestrogen also showed sex differences, although their results conform to this pattern. Oestrogenic effects on memory have not been

found consistently (Barrett-Connor and Silverstein, 1993) and one possibility worth exploring is that failures to find effects involved tasks that do not show reliable sex differences.

Our results did not support the hypothesis that oestrogen influences other cognitive tasks that show sex differences, including Mental Rotations and Controlled Associations. These findings disagree with those of a prior study of M-F transsexuals. In that study Mental Rotations was impaired and Verbal Fluency enhanced in M-F transsexuals receiving oestrogen treatment (Van Goozen et al., 1995). Possible explanations that could reconcile both sets of data include differing dosages and type of hormone used in the two studies. Few patients in the present sample were receiving anti-androgens, in contrast to Van Goozen's transsexual sample. However, both oestrogen and cyproterone acetate raise sex hormone binding globulin (SHBG) production leading to a reduction in levels of free testosterone. Also, Van Goozen used a 2-d Mental Rotations task, whereas we used a 3-d Mental Rotations task. As 3-d Mental Rotations shows a larger sex difference than 2-d Mental Rotation (Voyer et al, 1995), we used a more sensitive and powerful task to detect hormonal change than the previous study. Alternatively, the prior results might not be replicable. Consistent with our findings, a recent report failed to find an influence of oestrogen on

Verbal Fluency in a new group of M-F transsexual patients (Slabbekoorn, Van Goozen, Megens, and Gooren, 1998).

We found no evidence that duration or dosage of oestrogen treatment correlated with performance on memory or cognitive tasks. In contrast to our results for duration, research with rats suggests that short-term treatment with either high or low doses of oestrogen improves memory, whereas long-term treatment does not, suggesting that although dosage may not be important, duration of treatment is (Williams, 1996). Of course, similar differences in short- versus long-term effects in humans cannot be ruled out based on our data, because we might not have sufficient numbers of patients who have been treated for the most relevant lengths of time. Furthermore, the tasks used in our study do not correspond precisely to the spatial (as opposed to verbal) memory tasks used in rats. In regard to dosage, our results also cannot be interpreted to suggest that all differences in dosage are unimportant. Patients in this study were all treated with a hormone regimen sufficient to produce physical feminisation, and it is possible that lower doses of hormone would produce more graded effects.

Finally, we found no difference between patients on oestrogen and anti-androgen versus those on oestrogen without anti-androgen in any aspect of

memory or cognition. However, only five patients with the combined anti-androgen and oestrogen treatment were studied and a larger sample might be needed to detect effects.

Oestrogen treatment improved both immediate and delayed recall on the PAL. Oestrogen treatment, however, did not influence scores on Digit Span. Information processing models (Atkinson and Shiffrin, 1971; Baddeley and Hitch, 1974) highlight differences between these two memory tasks that could relate to their different sensitivity to oestrogen. Although both memory tasks were verbal, one involved the primary, working memory system with a time course of approximately 20-30 seconds (Digit Span) while the other could be classified as an episodic memory task, involving longer term storage (PAL). These different processing demands of the tests used might explain the dissociating influence of oestrogen. Factor analysis has also shown that the Digit Span task measures different aspects of memory than PAL (Kear-Colwell, 1977). However, interpreting our results in this framework remains speculative given the limited range of tests used.

Our study is the first we know of to examine the effects of administered oestrogen on memory in men and our findings suggest that these influences

are similar to those seen in prior studies of women. These findings are counter to those found in a prior study of normal variations in oestrogen and memory in men (Kampen and Sherwin, 1996). In that study oestradiol levels were related to visual memory but not verbal memory. This discrepancy might have resulted because the other study looked at naturally circulating levels of oestrogen. The much higher levels of administered oestrogen in the present study might produce different effects. Furthermore, it is not known if our findings would generalise to non-transsexual individuals. However, no abnormalities in chromosomal pattern, secondary sex characteristics, gonads or hormone levels have been found in transsexuals to distinguish them reliably from other males (Gooren, 1990). Although there are reports of a difference in a portion of bed nucleus of the stria terminalis (BSTc) between normal males and M-F transsexuals (Zhou et al, 1995; Kruijver et al, 2000), there is no evidence regarding differences in the cerebral cortex.

In summary, the results suggest that oestrogen treatment in M-F transsexuals improves performance on a verbal memory task that shows a sex difference (PAL), but not on a verbal memory task that does not (Digit Span). These results are similar to those reported previously for oestrogenic influences on memory in women and suggest that the proposed

ameliorating influences of oestrogen on memory disorder in women may apply to men as well. In contrast to results for memory, oestrogen did not affect performance on other cognitive measures, including two that show sex differences (Mental Rotations and Controlled Associations) and one that does not (Vocabulary). Additional research is needed to determine why prior findings on women suggesting that oestrogen impairs performance on Mental Rotations and improves performance on Controlled Associations, were not supported in our sample. One possibility is that oestrogen has different effects on these abilities in men versus women.

CHAPTER 3: SEX DIFFERENCES IN SELECTED MEMORY

TASKS. A META-ANALYTIC REVIEW.

3.1. CHAPTER SUMMARY

Past research suggests hormonal involvement in cognitive functions related to memory. This review investigates whether differences in the type of memory tasks used influence results. Specifically, based on evidence from other species indicating that gonadal hormones influence characteristics that show sex differences, it was hypothesised that only those memory tasks that show sex differences would be influenced by oestrogens. This meta-analysis looks at the magnitude and reliability of sex differences in memory tests employed in oestrogen and memory research and investigates factors other than sex that might influence Effect Size (ES). We found some evidence that age of subjects may influence the ES obtained on the Logical Memory (LM), Visual Reproduction (VR) and Object memory / Location memory tasks. Furthermore we found year of publication to be associated with LM. Results are discussed with reference to changing levels of gonadal hormones with age and their possible impact on memory abilities alongside moderating factors other than sex that influence ES.

3.2. INTRODUCTION

The literature review in Chapter 1 suggests hormonal involvement in cognitive functions related to memory. An association between oestrogen and specific tests of memory has been reported in postmenopausal women undergoing ERT and in normally cycling women at different phases of the menstrual cycle. It also appears that oestrogen can change brain activity in areas implicated in learning and memory. However findings for both neural and cognitive changes are inconsistent across studies (Barrett-Connor and Kritz-Silverstein, 1993; see Sherwin 1996; 1997; 1998 for reviews).

Haskell, Richardson and Horwitz (1997) attempted to quantitatively summarise the magnitude of oestrogenic influences on memory and cognition from past research looking at memory and cognitive performance in postmenopausal women taking ERT. They analysed characteristics of these studies to locate possible factors responsible for the inconsistent findings among studies. Studies reviewed used retrospective or prospective reports to monitor memory and cognition. They also used different procedures, different participants, different types of oestrogens and different durations of usage. They suggested inconsistent findings among studies might be due to these factors alongside the different measures used

to demonstrate oestrogenic effects. They concluded that the lack of comparability among these small numbers of studies available for review precluded a quantitative synthesis of the literature, therefore, a qualitative review of these studies resulted.

Subsequent evidence also suggests that the use of different measures could be important in explaining these inconsistent findings across studies. For example, Shaywitz, Shaywitz, Pugh, Fulbright, Skudlarski, Mencl, Constable, Naftolin, Palter, Marchione, Katz, Shankweiler, Fletcher, Lacadie, Keltz and Gore (1999), used MRI to examine how oestrogen treatment influences brain activation in brain regions thought to be involved in both visual and verbal memory. They found that oestrogen increased activation. Changes in performance, however, were not observed. They suggested that the failure to detect a change in performance coinciding with changes in brain activation patterns may be due to possible ceiling effects in the memory tests used.

To monitor the effects of oestrogen on memory, researchers might benefit from having a compendium of tests that are sensitive to changes in oestrogen levels. Specifically, based on evidence from other species indicating that gonadal hormones influence characteristics that show sex

differences, it was hypothesised that only those memory tasks that show reliable sex differences are sensitive to oestrogenic influence (Collaer and Hines, 1995).

The aims of the present review were: i) to quantitatively review a selection of memory tests which have been used in oestrogen and memory research to assess whether these tests show reliable sex differences and, if so, the magnitude of the sex differences; ii) to ascertain whether sex differences in memory reflected the verbal / visual-spatial dichotomy in general cognitive performance, such that females excel on verbal memory tests and males excel on visual-spatial memory tests; iii) to investigate study characteristics that might influence ES for sex, such as sample size, age of sample, year in which research was published, type of participant and whether studies were published or not.

3.3. METHOD

3.3.1 Literature Searches

Studies were located through the following computer databases: BIDS (Bath Information Data Service - Science and Social Science indexes): years 1981-2002; Dissertation Abstracts International: years 1960-2002; Medline: years 1966-2002; PsycINFO: years 1967-2002 and ERIC (Educational Resources Information Centre): years 1970-2002; The following key words were used: sex / gender AND memory / verbal memory / visual memory / Paired Associate Learning / Visual Reproduction / Object / Location / Digit Span / Corsi Spatial Span / Logical Memory / story recall / paragraph recall. Authors of specific memory tests (e.g., Silverman and Eals, 1992) were also contacted for unpublished and normative data.

Criteria for inclusion

Only memory tasks with at least 5 different samples of participants were included in this review. This minimum allows for a meaningful test of the heterogeneity of ESs for sex differences in these tasks. The memory tests reviewed were selected on the basis of use in past research on oestrogen

and memory whether they demonstrated oestrogenic influence or not. To date, the Corsi Spatial Span test, has not been used in oestrogen and memory research but was selected as a visual-spatial analogue of the verbal Digit Span test.

Studies were excluded from the meta-analysis if they fulfilled one or more of the following criteria: i) If they reported insufficient information for the computation of ESs (N, means, SDs or F statistics). ii) If participants were normal but put under conditions which might alter normal responses (e.g., Messier, Gagnon and Knott (1997), in which subjects were tested after fasting)). iii) If participants were neurologically damaged (e.g., Ryan, Paolo, Miller and Morris (1997)); neuropsychologically impaired (e.g., Naugle, Chelune, Cheek, Luders and Awad (1993), who tested subjects with epilepsy and left or right hemisphere dysfunction)); had a history of seizures (e.g., Strauss, Wada and Goldwater (1992)); or had been involved in automobile accidents producing attentional deficits (e.g., Di Stefano and Radanov (1995)). iv) If results were collapsed across gender (e.g., Ingram (1995); Troster, Stalp, Paolo, Fields and Koller (1995); Rasile, Burg, Burright and Donovan (1995)). v) If scores on several tests were not reported individually but only as a combined score reflecting a general

verbal memory score (e.g., Albus, Hubmann, Mohr, Scherer, Sobizack, Franz, Hecht, Bormann and Walheim (1997)).

3.3.2. Tests evaluated

Verbal Memory Tests

Logical Memory (LM) Wechsler Memory Scale (WMS). This subtest consists of two brief stories that are read to the participant. After each one, the participant retells the story from memory. Following a delay of 30 minutes the participant is again asked to relate each story, as a measure of delayed recall.

Verbal Paired Associate Learning (PAL) (WMS). The participant learns ten word pairs, six of which reflect easy associations (e.g., metal-iron) and four of which are more difficult (e.g., crush-dark). The participant is required to recall the word (e.g., iron) that is paired with the cue word (e.g., metal). There are 3-6 learning trials and a single delayed recall trial after 30 minutes.

Digit Span (DS) (WMS). This requires the participant to repeat series of digits in a predetermined order. The number of digits increases with each item. The task is then repeated with the participant instructed to repeat the digits in reverse order.

Visual / Spatial Memory Tests

Object memory and Location memory (Silverman and Eals, 1992).

First, the participant is presented with an array of objects drawn on a page for one minute. A second array is then shown with the original objects as well as some others. The participant crosses out all those objects that were not present in the first array (measure of Object memory). Subsequently, a third array is shown featuring all the objects from the first array with some of the object locations changed. The participant is then asked to indicate which have changed locations and which have not (measure of Location memory). The following variants of the paper and pencil form of this task were also included in the meta-analysis:

i) Naturalistic settings (Silverman and Eals, 1992).

This variation uses actual objects instead of drawings of objects. Some conditions involve instructing participants to learn the objects and their locations in a room (directed learning), whereas other conditions require participants to stay in the room with no instruction to learn the objects or their locations (incidental learning).

ii) Uncommon objects (Eals and Silverman, 1994).

This variation uses uncommon rather than common objects. The same paper and pencil procedures are used as in the original form. Naturalistic settings as described above are also used with uncommon objects.

iii) Location Shift (James and Kimura, 1997).

This variation adapts the original task by shifting the location of the objects. Two response arrays have been designed and are used as alternate forms to replicate the effect of shifting locations of the original objects. Each participant receives only one of the response arrays. In the first, the locations are shifted to different places (12 of the 27 objects are moved to locations previously unoccupied by an object in the first presentation array). In the second array, the locations are shifted to different places (14 of the 27 objects are moved to locations previously unoccupied by an object in the first presentation array).

iv) Computer administration array (James and Kimura, 1997).

This variation compares paper presentation of the original task versus computer administration. The presentation / response conditions are arranged in three ways i.e., paper presentation with paper response (paper / paper); computer presentation with paper response (computer / paper) and computer presentation with computer response (computer / computer).

Visual Reproduction (VR) (WMS). The participant is shown a simple geometric design for 10 seconds. The design is then removed and the participant is asked to draw the design as accurately as possible from memory. There are 3 separate designs and a delayed recall trial after half an hour.

Corsi Spatial Span (Milner, 1971). This requires the participant to touch a series of coloured squares in a predetermined order, which is first demonstrated by the examiner. The number of squares touched increases with each item. The task is then repeated with the participant instructed to touch the squares in reverse order. To date, this has not been used in oestrogen and memory research, but was included in this meta-analysis, as this test is a visual-spatial analogue of Digit Span.

3.3.3. Recorded variables

For each study the following study characteristics were recorded to investigate the magnitude of ES for sex.

i) The sample size for each study was used to weight the ES obtained, as results obtained from a larger sample are more reliable than those obtained from a smaller sample (see Table 14 for range of sample sizes). ii) The type of subject population, that is whether the sample in each study was drawn from a general community based or student population (see Table 14 for ratio of subject population types). iii) The mean age of the male and female sample was recorded as deterioration in some memory processes occurs with aging (Drachman, 1976; Botwinick, 1977). Where this was reported for males and females separately, the average of these two measures was used to give an approximate combined mean age for the two groups (see Table 14 for mean age range of studies). iv) The year of publication of study was examined to identify if sex differences are stable across time (see Table 14 for range of years of publication). v) Finally, due to the bias in the literature to publish research studies yielding significant findings, the studies were coded according to whether they were published in a peer reviewed journal or as unpublished data from part of an undergraduate,

Masters or Doctoral thesis (see Table 14 for ratio of published / unpublished data).

3.3.4. Procedure

For LM, VR and Verbal PAL tests, researchers report scores for immediate, delayed recall or a composite score combining immediate and delayed recall. ESs were grouped according to these 3 ways of scoring.

Cohen's d (1969) was used as a measure of ES and calculated from the Means and SDs for males and females. The difference between these two group means was divided by the pooled standard deviation. Multiple ESs were calculated for the same test from the same study if several samples were included (e.g., 5 ESs were calculated in a study using 5 age groups (Iverson, 1993)). ESs were then averaged over the different studies using each test. As Cohen's d is suggested to have limited value in terms of comprehensibility to non-statisticians (McGraw and Wong, 1992), the Common Language (CL) statistic, which is complimentary to Cohen's d , was calculated to aid interpretability. The CL statistic gives a percentage likelihood that a score sampled from one group will be greater than a score

sampled from the other group. As a guide, if there is no sex difference this will equal 50.

Homogeneity of ESs was calculated for each comparison using a statistical formula (Rosenthal and Rubin, 1982). The formula provides a statistic with a chi-square distribution with $K - 1$ df (where K = the number of studies). If this statistic is significant, the ES for the studies summarised for each test is heterogeneous.

Correlational statistics were used to assess the association of the recorded variables to the ES obtained. See Table 15.

Due to the bias to publish reports finding sex differences over similar studies not finding sex differences (the 'file drawer' problem'), Rosenthal's formula (1979) was used to determine the number of studies that would be needed to reverse the conclusion of a significant difference (fail safe method). The criterion value for the fail safe method was set at $p = .1$. Therefore the value calculated in Table 11 translates to the number of additional studies that would be required to bring the average ES to .1. This was calculated only for the tests that showed an ES for a sex difference that differed significantly from zero.

3.4. RESULTS

Descriptive statistics for all studies included in the meta-analysis are presented in Table 10. These include mean ES (d), weighted ES (d'), ranges of d, CI (Confidence Intervals) and CL (Common Language Statistics). Magnitude of ES (d) and (d') are also illustrated in Figures 3 and 4. According to Cohen (1977), ESs of .20, .50 and .80 indicate small, medium, and large effects, respectively, and this criterion was used to assess the magnitude of sex differences. ESs of .15 - .19 were interpreted as very small, and ESs below .15 were interpreted as negligible.

Table 10: Descriptives of studies collected for all memory tests

	N	d	SD	d'	Median (d)	Range (d)	CI	CL (%)
Object memory	13	.26	.32	.26	.31	-.65 to .68	.07 to .46	60
Location memory	18	.53	.48	.44	.62	-.22 to 1.41	.30 to .77	66
Verbal PAL (composite)	19	.21	.19	.20	.21	-.24 to .63	.12 to .30	86
Verbal PAL (immediate recall)	6	.12	.18	.30	.14	-.14 to .35	-.07 to .30	55
Verbal PAL (delayed recall)	5	.07	.19	.06	.09	-.19 to .33	-.17 to .30	56
DS	34	-.01	.29	.02	.04	-.62 to .71	-.11 to .09	50
Corsi Spatial Span	9	-.20	.18	-.29	-.23	-.41 to .10	-.34 to -.06	56
LM (composite)	16	.00	.29	-.11	-.03	-.43 to .43	-.15 to .16	55
LM (immediate recall)	24	.13	.49	.00	.10	-.78 to 1.29	-.08 to .34	61
LM (delayed recall)	20	.09	.48	-.11	.13	-.71 to 1.00	-.13 to .32	58
VR (composite)	11	-.27	.21	-.23	-.28	-.58 to .01	-.42 to -.13	55
VR (immediate recall)	19	-.19	.54	-.11	-.20	-1.48 to 1.00	-.45 to .07	63
VR (delayed recall)	14	-.07	.54	-.17	-.13	-.84 to 1.33	-.38 to .24	56

Note: N (no. of studies collected); d (Cohen's d); d' (weighted d by sample size); Positive

ES show differences favoring females. CI (95 % Confidence Interval for d). CL (Common Language Statistic) = the percentage of those sampled from one sex that will be greater than a score sampled from the opposite sex (in the indicated direction of d).

Figure 3: Unweighted ES for each test

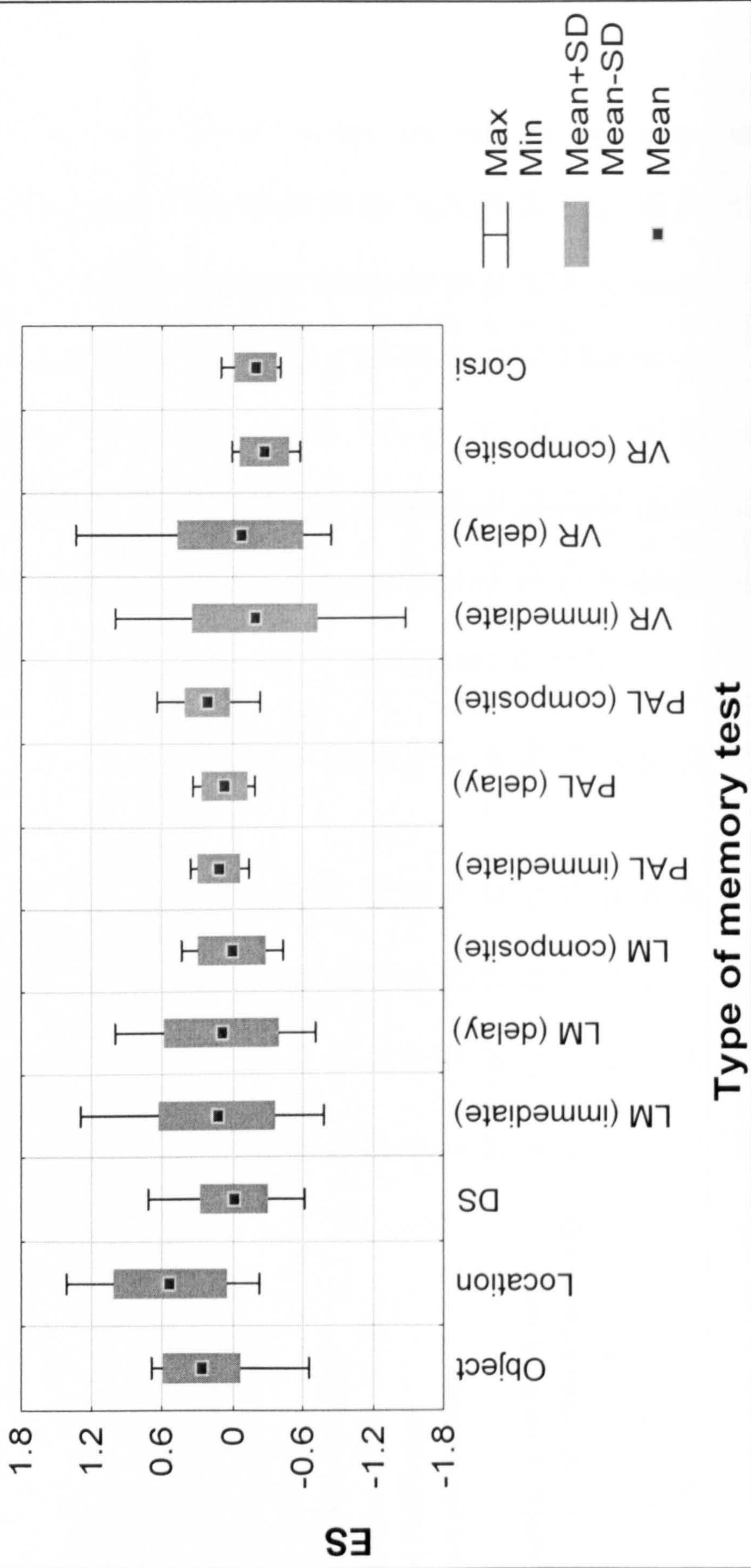
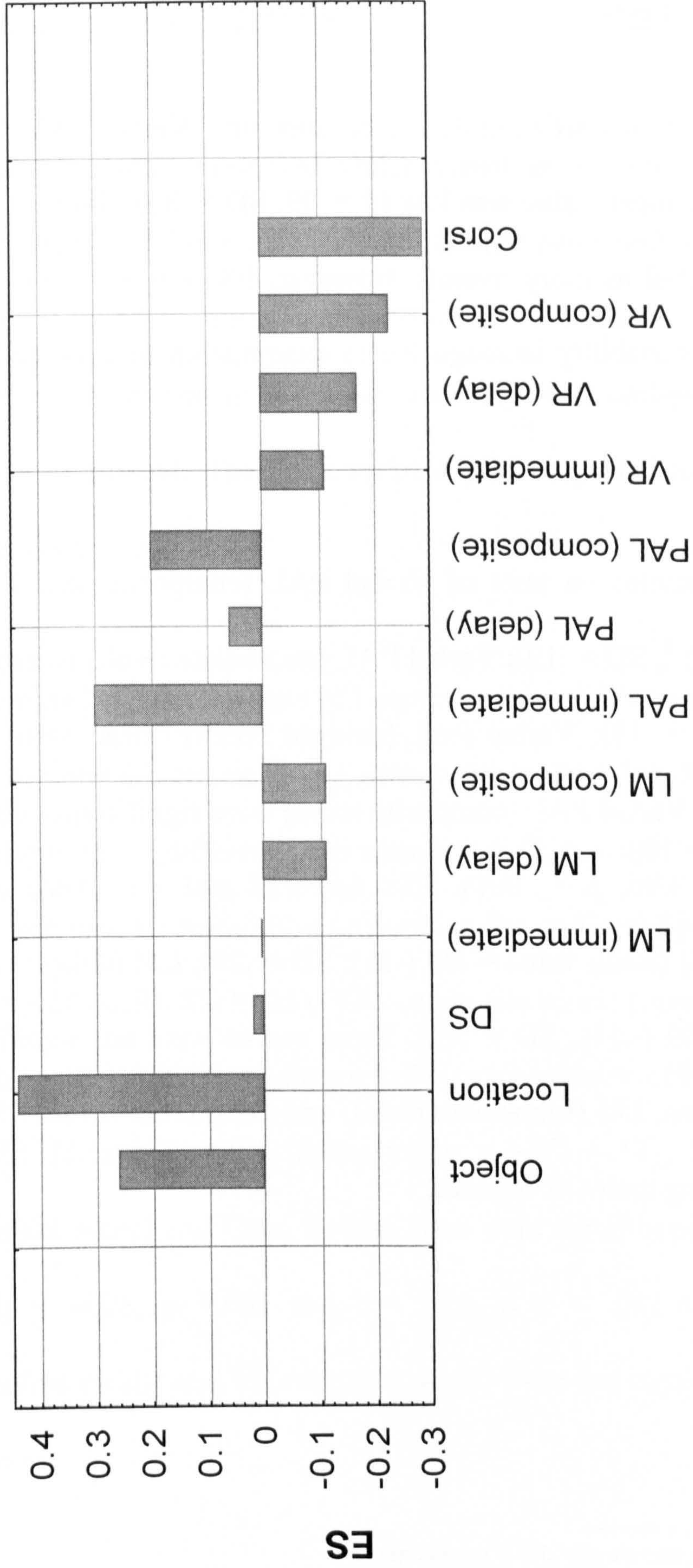


Figure 4: Weighted ES for each test



Verbal Memory Tests

For the 124 reports classified under verbal memory (Verbal PAL, DS and LM), ESs for the mean value was low ($d = .08$, $SD = .36$), showing no sex difference in verbal memory overall. However, ESs ranged from $-.78$ to 1.29 . The large variability in range led to examination of average ES for each test.

ESs favoured females on tests of Verbal PAL (composite score) (mean value = $.21$ ($.20$)⁸, $SD = .19$); Verbal PAL (immediate recall) (mean value = $.12$ ($.30$), $SD = .18$); Verbal PAL (delayed recall) (mean value = $.07$ ($.06$), $SD = .19$). Verbal PAL (composite score) were significantly different from zero ($t = 4.96$, $p < .001$). ESs favoured males on tests of LM (composite score) (mean value = $.00$ ($-.11$), $SD = .29$); LM (delayed recall) (mean value = $.09$ ($-.11$), $SD = .48$). These scores were not significantly different from zero. LM (immediate recall) and DS did not reveal ESs in a direction favouring males or females.

⁸ ES weighted by sample size are provided in parentheses.

Visual / Spatial Memory Tests

For the 84 studies classified under visual or spatial memory (Object memory and Location memory; Corsi Spatial Span and VR), ESs for sex differences based on the mean was low ($d = .04$ ($SD = .52$), showing no overall sex difference in the visual memory tests collapsed. ESs ranged from -1.48 to 1.41 . The large variability in range led to examination of average ES for each test.

ESs favoured females on tests of Location memory (mean value = $.53$ ($.44$), $SD = .48$) and Object memory (mean value = $.26$ ($.26$), $SD = .32$). These were significantly different from zero ($t = 4.73$, $p < .001$ and $t = 2.95$, $p < .01$, respectively). Overall ESs favoured males on Corsi Spatial Span (mean value = $-.20$ ($-.29$), $SD = .18$), VR (composite score) (mean value = $-.27$ ($-.23$), $SD = .21$), VR (immediate recall) (mean value = $-.19$ ($-.11$) $SD = .54$) and VR (delayed recall) (mean value = $-.07$ ($-.17$), $SD = .54$). VR (composite score) and Corsi Spatial Span were significantly different from zero ($t = -4.28$, $p < .001$ and $t = 3.21$, $p = < .01$, respectively). VR (immediate recall) and VR (delayed recall) were not significantly different from zero.

As variants of the original Object memory and Location memory were collapsed in the analysis, Tables 8 and 9 separate the different types of variations of this task to ascertain if this influences magnitude of ES.

For the Location-Shift condition the ES was 0 with a small range of .04 - .04. When these data were excluded from the analysis overall ES increased to .61 (SD = .46, range = .22-1.41). The highest ES obtained was from naturalistic settings that used direct instructions with common items (ES = 1.41 and 1.19). However, this may only be due to naturalistic setting conditions as the third highest ES was for incidental conditions in naturalistic settings (ES = 1.07).

Table 11: Significance, Homogeneity and Fail Safe statistics for ES by memory test.

	Significance of d (paired t-test value)	No. of Fail Safes (using d †)	No. of Fail Safes (using d' †)	Homogeneity statistic (∇)
Object memory	2.95 ***	20.8	20.8	22.62***
Location memory	4.73 ***	77.4	61.2	52.24***
Verbal PAL (composite)	4.96 ***	20.9	19	14.14
Verbal PAL (immediate recall)	1.60	-----	-----	8.33*
Verbal PAL (delayed recall)	0.80	-----	-----	2.21
DS	-.22	-----	-----	66.40***
Corsi Spatial Span	-3.21 ***	9	17.1	12.24*
LM (composite).	.07	-----	-----	36.98 ***
LM (immediate recall)	1.01	-----	-----	73.91***
LM (delayed recall)	.55	-----	-----	62.17***
VR (composite)	-4.28 ***	18.7	14.3	26.59***
VR (immediate recall)	-1.56	-----	-----	53.50***
VR (delayed recall)	-.51	-----	-----	74.24***

Note: * p < .1 ** p < .05 *** p < .001. † calculated only when significance of paired t-test < .05. Fail Safe method: criterion value used for d = .1 translates to the number of additional studies identified giving a small enough effect to bring the average ES to .1). ∇ Significance indicates heterogeneity of ES.

Table 12: ES for the variants of administration for Object memory

Type of administration	Mean ES	SD	Range	N
Paper and Pencil (PO) ¹	.39	.15	.18-.58	5
Paper and Pencil (P) ²	.27	.31	.18-.66	6
Incidental (I) ³	.35	.35	.09-.68	10
Directed (D) ⁴	.02	.59	-.65-.43	3
Common Objects (CO) ⁵	.41	.15	.18-.68	9
Uncommon Objects (UO) ⁶	-.04	.41	-.65-.19	4
Published (PUB) ⁷	.24	.36	-.65-.68	10
Unpublished (UNPUB) ⁸	.37	.20	.18-.58	3

Note: ES for each type of administration includes other types of administration.

1. (PO) original Paper and Paper task (Silverman and Eals, 1992)
2. (P) All Paper and Pencil tasks including (I), (CO) and (UO) conditions
3. (I) All incidental tasks including (PO), (UO), (CO) and naturalistic conditions
4. (D) All directed tasks including (PO), (UO), (CO) and naturalistic conditions
5. (CO) All common objects tasks including (PO), (I), and (D) and naturalistic conditions
6. (UO) All common objects tasks including (PO), (I), (D) and naturalistic conditions
7. (PUB) All published studies irrespective of condition
8. (UNPUB) All unpublished papers. (PO) conditions only

Table 13: ES for the variants of administration for Location memory

Type of administration	Mean ES	SD	Range	N
Paper and Pencil (PO) ¹	.29	.31	-.19-.68	6
Paper and Pencil (P) ²	.26	.34	-.19-.66	9
Incidental (I) ³	.49	.38	-.19-1.07	15
Directed (D) ⁴	.79	.89	-.22-1.41	3
Common Objects (CO) ⁵	.57	-.19	-.19-1.41	15
Uncommon Objects (UO) ⁶	.38	.52	-.22-.71	3
Published (PUB) ⁷	.63	.46	-.22-1.41	15
Unpublished (UNPUB) ⁸	.10	.33	-.19-.45	3
Location Shift (LS) ⁹	.00	.06	-.04-.04	2
Computer (C) ¹⁰	.72	.19	.59-.86	2

Note: ES for each type of administration includes other types of administration.

- 1 (PO) original Paper and Paper task (Silverman and Eals, 1992).
- 2 (P) All paper and pencil tasks including (PO), (I), (D), (CO) and (UO) conditions.
- 3 (I) All incidental tasks including (PO), (UO), (CO), (C), (LS) and naturalistic conditions
- 4 (D) All directed tasks including (C), (UO) and naturalistic conditions.
- 5 (CO) All common objects tasks including (PO), (I), (C), (LS) (D) and naturalistic conditions
- 6 (UO) All common objects tasks including (PO), (I), (D) and naturalistic conditions
- 7 (PUB) All published studies including all conditions
- 8 (UNPUB) All unpublished papers. (PO) conditions only
- 9 (LS) including (PO) and (CO)
- 10 (C) including one (PO) condition.

Factors influencing ES for sex differences

Table 14 shows summary statistics of these factors.

Table 14: Summary statistics of study characteristics

	Mean age range	Sample size range	Year of publication	Student / General Population ratio	Published / Unpublished ratio
Object memory	8-33	40 - 204	1992-1999	10 / 3	10 / 3
Location memory	8-33	20-217	1992-1999	15 / 3	15 / 3
Verbal PAL (composite)	25-75	58-112	1988-1994	0 / 20	20 / 0
Verbal PAL (immediate recall)	33.-72	45-1805	1990-1999	0 / 6	4 / 2
Verbal PAL (delayed recall)	33.-72	45-140	1990-1999	0 / 5	3 / 2
DS	7-84	24-1868	1972-1999	9 / 25	24 / 10
Corsi Spatial Span	7-53	63-1355	1980-1993	4 / 5	9 / 0
LM (composite)	25-75	58-1805	1979-1994	0 / 16	16 / 0
LM (immediate recall)	11-72	16-1805	1983-2002	6 / 18	21 / 3
LM (delay recall)	11-72	16-1805	1986-2002	4 / 16	19 / 1
VR (composite)	25-86	94-619	1979-1993	0 / 11	11 / 0
VR (immediate recall)	11-86	16-1805	1983-2002	3 / 16	16 / 3
VR (delay recall)	11-86	16-619	1986-2002	3 / 11	13 / 1

Table 15: Correlations of unweighted d with study characteristics

	Sample size	Year of publication	Mean age of sample	Type of participant	Whether published or not
Object memory	-.03	.01	.06	-.18	.18
Location memory	-.22	-.61***	-.38	.32	-.32
Verbal PAL (composite)	-.67***	-.21	.18	(GP)δ	(PUB)δ
Verbal PAL (immediate recall)	.65	.21	-.01	(GP)δ	-.10
Verbal PAL (delayed recall)	-.16	.13	-.57	(GP)δ	.44
DS	.08	.05	-.25	.25	.30
Corsi Spatial Span	-.51	.58	-.22	-.27	(PUB)δ
LM (composite)	-.21	-.08	.52**	(GP) δ	(PUB) δ
LM (immediate recall)	-.10	.43**	.21	-.27	-.16
LM (delayed recall)	-.16	.38	.14	-.28	-.05
VR (composite)	.25	.21	.77***	(GP) δ	(PUB) δ
VR (immediate recall)	.08	.02	-.01	.10	-.35
VR (delayed recall)	-.17	-.12	-.45	.23	↔

note: * = $p < .10$ ** = $p < .05$ *** = $p < .01$ **** = $p < .001$.

For type of subject, positive values represent students influencing magnitude of ES.

δ Cannot be computed because this variable is constant. Type of subject: (GP) samples consisted of General Population only (S) samples consisted of Students. Whether published or not: (PUB) all published data. ↔ Cannot be computed, as the uneven splits of the categories do not fulfil the assumption required for statistical analysis. i.e., 10% in one category 10% versus 90% in the other (Tabachnik and Fidell, 1996).

Homogeneity of ES

Figure 3 illustrates the diversity in range of ES for each test. Verbal PAL (composite and delayed recall) scores were significantly homogenous, such that the studies collected showed similar ESs. All other tests showed significant heterogeneity, such that the studies collected dissimilar ESs (see Table 11). As ESs varied significantly within each test, it suggests that sex differences are not stable or reliable and that, in the present review, other factors explain the differences among studies in ES. This does not mean that the overall ES is meaningless, but that closer examination of the studies is needed to increase understanding and develop new hypotheses about these other possible factors.

Table 15 shows correlational data for associations between the unweighted ES and with the study characteristics of sample size, year of publication, mean age of sample, type of subject and source of research (whether the data was published or unpublished).

Sample Size

A negative correlation was found between ES and Verbal PAL (composite score) ($r = - .67, p < .01$), suggesting that the smaller the sample size the larger the sex difference. Further investigation of this by scatterplot suggested this association might be due to an outlier. One study (Tomer, Larrabee and Crook, 1994) gave an ES of .63, based on a sample of 58 individuals. It was decided that a sample size of 58 was not sufficiently small to exclude this outlier. Even when this study was excluded the correlation between sample size and ES remained significant ($r = -.65, p < .05$). Whilst this appears to suggest that the association was not caused by the outlier, examination of the other studies revealed that out of the other 18 studies included for this test, 17 employed a sample size of 100 and 1 other study, a sample size of 103. Therefore it is questionable to make interpretations of an association between sample size and ES when the data are of a restricted range. To provide an accurate description of the relationship between sample size and ES, a wide range of values in the data would be needed.

These data may relate back to the 'file drawer' problem mentioned earlier (Rosenthal, 1979), where there is a tendency for studies supporting the null

hypothesis of no significant results to be rejected or not submitted for publication and left in the 'file drawer'. It is possible that such studies may have been characterised by small samples. Without access to these studies it is impossible to draw any inferences from the present review as to whether smaller samples are less reliable than findings from studies with larger samples.

The relationship between sample size and ES was not significant for any of the other tests, even when outliers were considered to determine whether they were obscuring any associations.

Year of publication

Feingold (1988) hypothesised that over the years, sex differences have decreased due to social changes. The present review found inconsistent support for this claim in regard to sex differences on memory tasks. The predicted negative relationship between year of publication and ES was found for Location memory ($r = -.61$ $p < .05$), suggesting this sex difference was disappearing over generations. However, this test was developed for use relatively recently. First and last reports included were from 1992 to 1999 respectively, therefore a wider range of years could help

the researcher to evaluate whether sex differences were disappearing over time. A positive association was found between year of publication and ES for LM (immediate recall) ($r = .43, p = < .05$). However, examination of the scatterplot does not suggest that as year of publication increases so does the sex difference (see Figure 7). It appears that during the late 1980s the sex difference marginally favours males. The sex difference reduces around the mid to late 1990s then the picture becomes more complex in the following years. Up to present, (year 2002) among the studies sex differences do not consistently favour either males or females. This possibly indicates there are other independent factors between studies determining sex differences in performance. Year of Publication varied more extensively for other tasks but did not relate to the magnitude of sex differences on any of these tasks.

Age

Past research implicating age as a confounding factor in sex difference research (Drachman, 1976; Botwinick, 1977) led to the examination of changes in the magnitude of ES with age. Mean sample age was used as an indicator of chronological age to investigate this relationship. Two of the tests showed ES to be significantly related to age, namely LM and VR (composite scores). With LM a significant positive association ($r = .52, p <$

.05) was found, however, examination of the scatter plot does not suggest that as age increases so does the sex difference (see Figure 5). It appears that during the mid 20s-40s the sex difference favours males. This sex difference reduces at approximately 50-60 years of age. The picture becomes more complex in the following years up to late 70s with the sex difference gradually reversing to favour females.

For the VR test, examination of the scatter plot also shows a positive association between age and magnitude of ES. This is misleading, as the ES does not actually increase with age. Instead, on the whole, the ES favours males with the sex difference decreasing with age, to near zero (see Figure 6).

Type of participant and source of data.

The type of participant, whether from a student or general population, may influence the magnitude of ES. For example, students on average are younger than the general population and are more accustomed to memorising things. Further, the source of the research, whether from a peer reviewed journal or from an unpublished academic dissertation, may relate to whether a sex difference has been detected. The latter point relates to the 'file drawer' problem outlined previously. These two variables were

dichotomously coded. The relatively small number of studies in the four groups leads to problems of statistical analysis. For these dichotomous variables, uneven splits between the two categories produce outliers (See Table 14 for ratios of these two variables). Statisticians advise 'deleting dichotomous variables with 90 / 10 splits between categories because the correlation coefficients between these variables and others are truncated and because the scores in the category with 10% of the cases are more influential than those in the category with 90% of the cases' (Tabachnik and Fidell, 1996). This prevented analysis of possible influences of these two variables for the majority of the tests. Where the categorical splits did fit assumptions for some tests neither type of participant or source of data influenced ES. For type of participant, tests that fitted these assumptions were Object memory and Location memory; DS, Corsi Spatial Span, LM (immediate and delayed recall) and VR (immediate and delayed recall). For source of data, tests that fitted these assumptions were Object memory and Location memory; DS, Verbal PAL (immediate and delayed recall), LM (immediate and delayed recall) and VR (immediate and delayed recall).

Figure 5: The relationship between LM and age

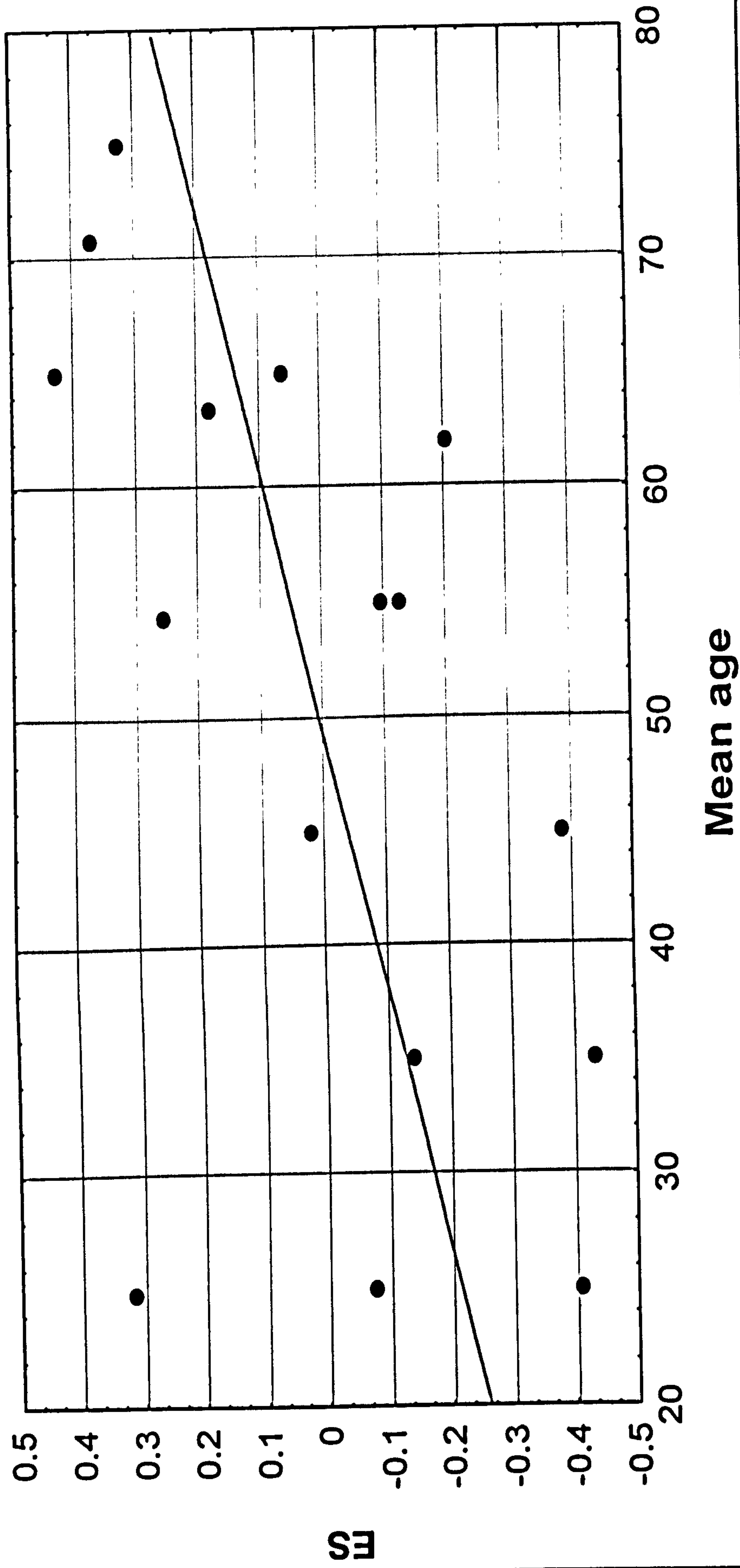


Figure 6: The relationship between VR and age

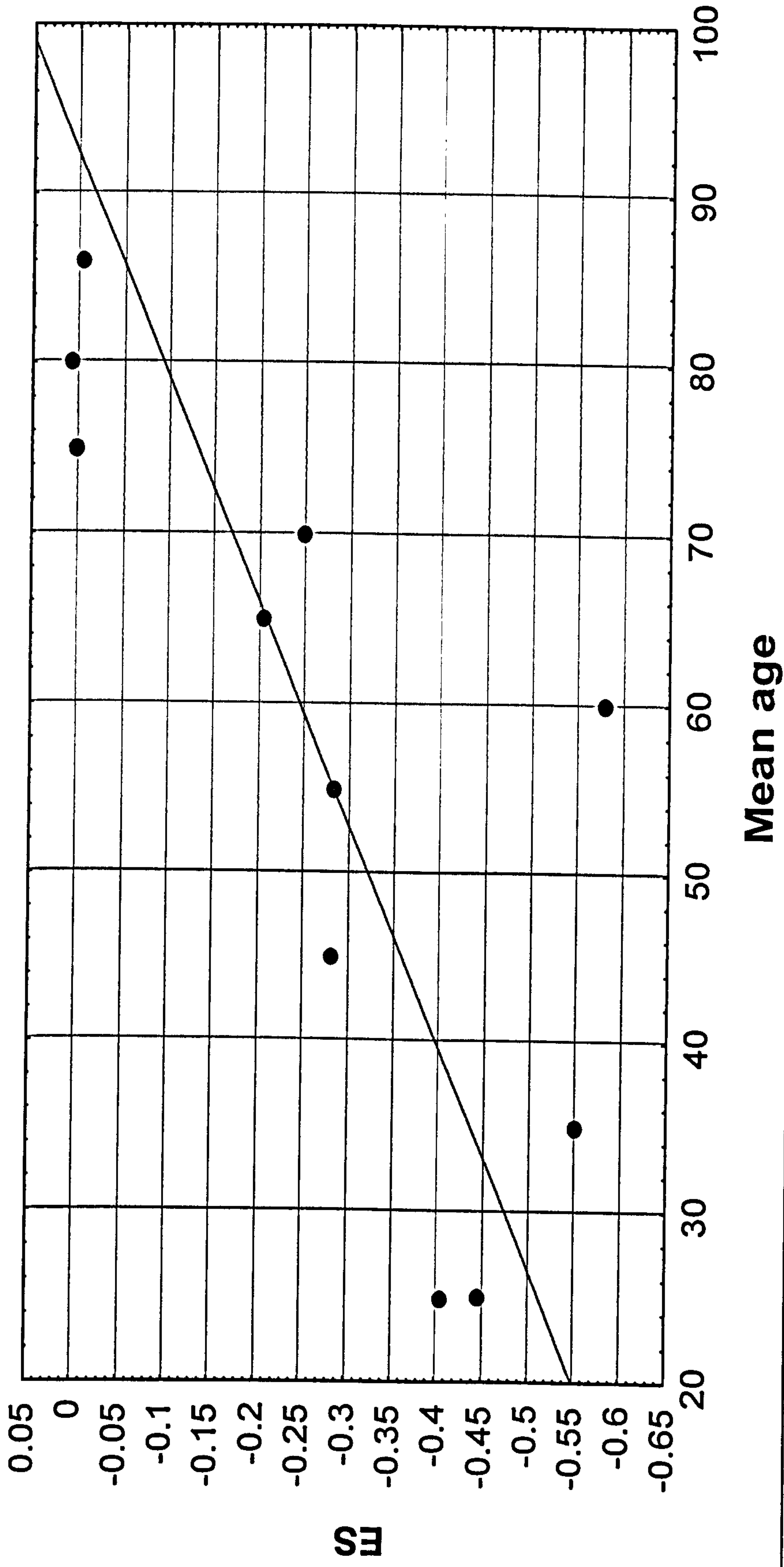
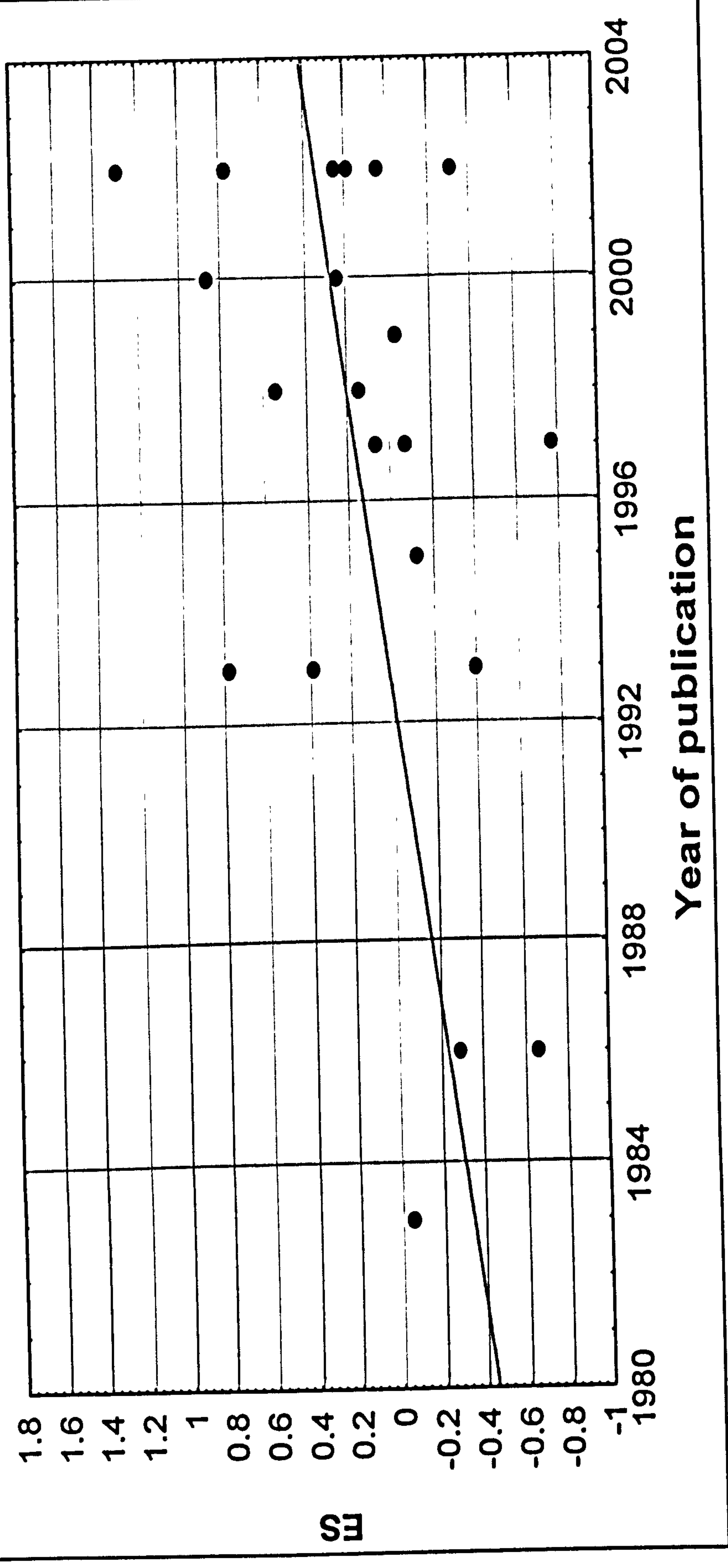


Figure 7: The relationship between LM and year of publication



3.5. DISCUSSION

In sum, some tests of verbal and visual-spatial memory favour females whereas others favour males. This review has attempted to address the 3 aims outlined in the introduction. Each will be discussed separately.

3.5.1. Magnitude of ES for the memory tests reviewed.

Sex Differences favouring females

Females excel in the verbal memory test, PAL, although the ES is smaller for the unweighted ES than the weighted ES. When ES is weighted for sample size the largest ES appears for PAL (immediate recall) ($d = .30$). Females also excel on the visual / spatial memory task, Object memory and Location memory. Due to the variations of the original paper and pencil task it was reasonable to calculate ESs for the different types of administration, assessing Object memory and Location memory.

Tables 8 and 9 show the ES for the different forms of this task. It appears that the consistent sex difference favouring females for Object memory was found for the incidental conditions rather than the directed conditions, irrespective of whether the objects were familiar or unfamiliar. It has been

suggested that this sex difference occurs as a 'perceptual style rather than a learning ability' (Silverman and Eals, 1992). However, for Location memory, naturalistic settings yield large ESs favouring females, whether with common or uncommon objects, incidental or directed conditions ($d = .69$ to $.14$). Similarly, computer forms give large ESs for Location memory, ($d = .59$ to $.86$). The Location – Shift condition for Location memory leads to no sex difference ($d = 0$). It has been suggested that the female advantage in the original task may be due to the 'importance of the object identity information' which is de-emphasised in the location exchange version (James and Kimura, 1997). Although the original paper and pencil form gives lower ESs for sex differences favouring females, most researchers use paper and pencil forms for ease of administration, particularly in a battery of psychometric tests. Furthermore higher oestrogen levels during the menstrual cycle have been associated with higher performance using this form of administration (Gaulin, Silverman, Phillips and Reiber, 1997). This suggests that the paper and pencil form of administration is sensitive to changes in oestrogen levels and would be useful in a compendium of tests to examine oestrogenic influences on memory.

Sex differences favouring males

Figures 3 and 4 illustrate that overall males excel on visual memory tasks such as VR and Corsi Spatial Span, yet also on a verbal memory task, LM, albeit with a small ES.

Tests showing no sex differences

DS consistently showed no sex difference ($d = -.01$ and weighted $d = .02$). This may explain previous findings in Chapter 2 where M-F transsexuals taking oestrogen treatment did not differ from those awaiting treatment on this task. To test the hypothesis that gonadal hormones influence only tasks that show sex differences, DS may be a useful control task.

To assess whether the tests show reliable sex differences it is important to consider the calculated fail safe numbers (Table 11). These were calculated for all those tests that showed sex differences significantly different from zero. Rosenthal (1980) suggested that a fail safe number reaching a value of $5K + 10$ (K being the number of sampled studies) indicates combined results resistant to the 'file drawer' problem. None of these tests proved resistant to the 'file drawer' problem. This implies that the ESs obtained for

each test that was significantly different from zero could have been biased. Therefore to be confident that these studies are representative of the research in the field is premature. Hypothetically, if all unpublished data were to be included for the tests in this review, ESs may actually not be significantly different from zero.

3.5.2. Does the sex difference favouring males or females reflect the visual- spatial / verbal dichotomy in general cognitive behaviour?

Sex differences favouring females only partially reflect the verbal / visual-spatial dichotomy in general cognitive behaviour. Females excel on Verbal PAL yet also on the spatial Object memory and Location memory measures.

Evolutionary psychology puts forward an explanation for why there is a female advantage for this spatial memory task. Silverman and Eals (1992) propose that this cognitive sex difference is due to evolved adaptive behaviours, which stem from primitive hunter-gatherer societies. Here women are predominantly reliant upon the use of objects and locations for foraging and gathering crops and these require memory for locations of crops that vary depending on the season of the year. Males evolved other

spatial skills that depend on hunting, such as successful navigation for food and competing for mates.

Herlitz, Nilsson, and Backman (1997) explored whether the sex difference was due to the particular process of memory or whether females excelled only in verbal memory tasks. They explored sex differences in semantic, primary, episodic and priming memory and found the sex difference occurred only with episodic memory tasks. Most tasks employed were of a verbal nature, however women outperformed men on face recognition and Object memory and Location memory tasks. They concluded that the sex difference was not due to this verbal advantage, but due to the differential processing employed between males and females.

3.5.3. Homogeneity of ES: Factors other than sex that might influence sex differences.

ESs for the Verbal PAL task (composite and delayed recall scores) were significantly homogenous ($p < .05$), such that the studies collected showed similar ESs. Also, the Corsi Spatial Span was close to conventional level of significance ($p < .1$). Although we can be preliminarily confident that there are sex differences between males and females on these tasks, larger

numbers of studies would be need to support these hypotheses. All other tests, however, showed significant heterogeneity, leading to the assumption that there are factors other than sex, which are causing such variation among ESs calculated within each memory test.

The attempt to achieve homogeneity of ES considered the influence of possible moderating variables such as age, year of publication, sample size, type of participant and source of study. This was the third aim of this review. Age of the participants appeared to influence ES in the following three tests:

Age as a factor influencing ES for sex difference:

i) Object memory and Location memory

One study suggests that age may influence ES obtained on the Object memory and Location memory task. Miles and Poikei, (unpublished data, 1999) used the original paper and pencil version to compare prepubescent versus adult groups. For Object memory ES was .18 and .58, respectively. For Location memory ES was .02 and .45, respectively. Whilst this could suggest that activational influences of hormones play a role in this sex

difference, we cannot rule out a role for social changes at puberty in producing this effect. Another interpretation of this age effect could be that the task is too difficult for younger people, leading to floor effects in the data collected. Also, it is possible that the observed sex difference in this task might result from experience. One could speculate this finding may be due to an 'epoch', historical effect, such that people born from different decades had different educational experiences and this might have affected performance on this task. This would suggest that over the years, sex differences are decreasing and that it is not simply nature but nurture that is important for the expression of sexual dimorphism in memory and cognitive abilities. Therefore hormonal or environmental influences might be involved in the apparent emergence of this sex difference at puberty.

ii) LM (composite score)

The complex relationship between age of participants and ESs on LM described in the results section and depicted in Figure 5 can not be easily explained. With younger age groups the sex difference appears to favour males yet with increasing age the sex difference reverses, favouring females. More studies would be needed to see if this pattern of results remained stable. Furthermore, as far as hormonal explanations go, it is unclear from the studies selected whether older women were taking or not taking hormone replacement therapy. As previously mentioned in Chapter 1, women taking hormone replacement therapy may differ from those not taking hormone replacement therapy in performance on memory and cognitive tasks. This alone might complicate studies of sex differences in memory in older people. It would be helpful if future studies researching sex differences in memory in older people reported the hormonal status of female participants.

iii) VR (composite score)

Figure 6 represents the relationship between age and ES for VR. As previously mentioned, this visual memory task seems to favour younger males, yet with increasing age the sex difference declines to an ES of $d = 0$. There are possible hormonal explanations for this. In men testosterone declines with increasing age. As men have more testosterone than women, and this could be a cause of sex differences in cognition, it is possible that the reduction in testosterone led to the lack of sex difference.

There was inconsistent evidence that year of publication influenced ES for each test. A complex association between year of publication and LM (immediate recall) emerged, but subsequent research would be needed in to determine if this association remains stable (see Figure 7). Type of participant, whether from a student or the general population and whether the data was published or not, were problematic to analyse as the ratio splits did not always fulfill the necessary statistical assumptions. More studies would be needed to evaluate whether these factors influenced ESs.

Other possible factors influencing ES

There are other study characteristics, which this review did not examine that may contribute to variability in ES for sex differences on memory tests. In the introductory chapter, it was noted that oestrogen and progesterone levels vary during the menstrual cycle and may influence cognitive abilities that show sex differences. Research has also associated declining oestrogen levels in menopausal women with reduced performance on memory tasks.

Further recent research suggests that an individual's sexual orientation (Gladue, Beatty, Larson and Staton, 1990; Kimura, 1996; Hall and Kimura, 1995) and mood (Halbreich, 1997) may relate to cognitive function. Finally, as previously mentioned those who are left-handed have a more male stereotypical cognitive pattern (Bradshaw and Bradshaw, 1988; Lewis and Harris, 1990).

3.5.4. Limitations to this review

There are several reasons why further research is needed before confident conclusions concerning the ESs for sex differences in memory can be reached. Firstly, studies reporting sex differences in memory tend to be published when they show significant sex differences. Therefore the studies located for this review are likely to reflect those that escaped the 'file drawer' problem. This is reflected with the fail safe calculations which suggested that none of the sex differences could be confidently assumed to be significantly different from zero. Furthermore, for some studies data were often not reported separately for males and females. Either it was not the researcher's agenda or data was analysed by sex and no significant difference was found.

An additional limitation involves combining scores for different types of memory. For example, when scores for several of the tests involve immediate and delayed recall and researchers have combined these scores to make a composite, it is difficult to ascertain whether the sex difference lies in a particular memory store i.e., primary or secondary.

The lack of homogeneity may be due to the small number of studies available for each test. Maccoby and Jacklin (1974) concluded that gender differences in learning and memory are not significant. The present review indicates that certain tests might show sex differences favouring either females or males, however the fail safe findings place reliability of these findings in jeopardy. The available data suggest that there are medium sex differences favouring females on Location memory only and no medium sex differences favouring males or females on any other test. The remaining tests appear to show small to negligible sex differences. Age was identified as a potential factor to influence ES for sex differences in memory. Other factors such as sexual orientation, handedness and mood of participants may explain some of the inconsistencies in past research examining sex differences in memory, however such information was not available for this review.

Based on this and on evidence that hormones are most likely to influence tasks that show sex differences, Object memory and Location memory would seem the most likely candidates for hormonal effects, although tests showing small ESs in this review have been shown in past research to suggest oestrogenic effects, such as PAL, LM and VR. For example, PAL performance is maintained in surgically menopausal women treated with

oestrogen compared to placebo treated controls (Kampen and Sherwin, 1994). Also, LM improves in surgically menopausal women treated with oestrogen compared to baseline, whilst performance on this task remains the same in placebo treated controls (Phillips and Sherwin, 1992a). Furthermore, it has been reported that men with higher oestradiol levels perform better than men with lower oestradiol levels on VR (Kampen and Sherwin, 1996). The picture becomes confusing when a test that shows no sex difference e.g., DS has shown hormonal effects. When Carlson and Sherwin (2000; 1998) compared women taking ERT and those not taking ERT. Performance was higher in those taking ERT for DS forwards and backwards.

Therefore, there are questions that remain as to whether hormonal influences on memory are restricted to tests that show sex differences. Furthermore, given the lack of homogeneity among studies of sex differences as highlighted in this review, research available to the researcher may be merely the tip of the iceberg, with the remainder of research showing no sex difference or hormonal effect on memory is left in the file drawer.

**CHAPTER 4: THE ASSOCIATION BETWEEN OESTROGEN,
MEMORY, COGNITION AND MOOD: FURTHER
EXAMINATION.**

4.1. INTRODUCTION

As outlined in Chapter 1, it has been observed that oestrogen levels can influence memory and cognition in animals and humans. Further, beneficial effects of oestrogen on mood have been reported in postmenopausal women undergoing Oestrogen Replacement Therapy (ERT) compared to non-treatment controls. An assumption from past research is that the gonadal hormones, including oestrogen, influence only behaviours that show sex differences.

In Chapter 2 the association between administered oestrogen and performance on verbal memory and other cognitive tasks was examined. Partial support for the hypothesis that oestrogen influences only those tasks that show sex differences was found. Selective effects on verbal memory were found for a small sample ($n = 29$) of Male-to-Female (M-F) transsexuals who received oestrogen treatment in advance of SRS. When compared with a group of M-F transsexuals who had been awaiting

oestrogen treatment (n = 30), transsexuals taking oestrogen showed enhanced performance on a verbal memory task which showed a sex difference, but did not outperform the control group on a verbal memory task which showed no sex difference. However, the results did not support the existence of oestrogenic effects on other cognitive tasks that show sex differences, such as Mental Rotations and Controlled Associations. Furthermore the two groups did not differ on any of the mood measures.

Whilst this study shows some indication that oestrogen may influence some cognitive abilities in adult men, the present study intends to provide a more robust design to examine the association between oestrogen, memory, cognition and mood.

Aims of the present study were: i) to replicate previous findings using a between subjects design in a different population of M-F transsexuals i.e., a difference between oestrogen and non-oestrogen users on memory tasks, such as Verbal Paired Associate Learning (PAL); ii) to extend this design to incorporate other aspects of memory function, such as visual, spatial, Object memory and Location memory; iii) to use a within subjects design in a subset of this population to examine the effects of oestrogen on other aspects of cognition that show sex differences, such as visual-spatial ability

and Verbal Fluency; iv) to examine whether oestrogen only enhances abilities at which women excel on average and impairs those at which men excel on average or whether the effect of oestrogen is more global, irrespective of the nature of the task.

To examine whether there are activational influences of oestrogen on memory, cognition and mood, it is possible to test subjects both prior to hormone treatment and after treatment has begun. In addition, it is possible to test some patients during a period of hormone withdrawal of 8 weeks prior to surgery. This will allow me to determine if any observed cognitive changes associated with treatment would be reversed by hormone withdrawal and whether 8 weeks was sufficient time for these hypothesised changes to wear off. To control for practise effects in the repeated measures analyses, participants who have been established on oestrogen treatment will be tested on two occasions.

4.2. METHOD

4.2.1. Participants

One hundred and three genetic males desiring sex re-assignment as females and diagnosed as having Gender Identity Disorder, as defined in DSM IV (Diagnostic and Statistical Manual of Mental Disorders, 4th ed.) were tested. They were divided into 3 groups depending upon their stage in the treatment process.

Group 1 (off then on treatment condition). Patients were tested on the first occasion shortly before treatment (n = 40, mean age = 35.45 years, SD = 9.01). Of these patients, some were followed up and tested on a second occasion with a minimum of three months after oestrogen treatment commenced (n = 27, mean age = 37.46 years, SD = 8.76). The interval between test sessions varied from between 3 to 14 months and was dependent on their next consultation at the clinic as well as their availability.

Group 2 (on then off treatment condition). Patients were tested whilst on oestrogen treatment and subsequently tested on a second occasion, 8 weeks

after this treatment had been withdrawn, as prerequisite to SRS (n = 27, mean age = 39.93 years, SD = 9.75).

Group 3 (control group). As it would be unethical to use a placebo control in this experimental paradigm to test the effects of cross-sex hormones on memory, cognition and mood, another transsexual group were used as controls. Patients were tested on both occasions when established on hormone treatment for a minimum of three months at the time of the first test session. (n = 20, mean age = 40.30 years, SD = 7.50). Other patients were tested on one occasion but were unavailable for follow up at second test session (n = 16). The interval between test session varied from between 3 to 12 months and was dependent on their next consultation at the clinic as well as their availability.

Drop out rates for retest

Those patients who were unavailable for follow up from group 1 (n = 13) and group 3 (n = 16) either did not attend their subsequent consultation, found the tests too time consuming, or refused to participate with no reason given. Examination of these patients' medical records did not identify them as unsuitable candidates in terms of their transsexual status for these two groups. Those who did not participate in the second test from group 1 were

significantly younger than those from group 1 who did participate in a second test session ($F(1, 39) = 5.00, p = .03$). They did not differ in level of education. Those from group 3 who did not participate in the second test session did not differ from those who did participate in a second test session in age or level of education. They also were comparable in type of hormone they were taking.

All participants were paid volunteers and were recruited through the Gender Identity Clinic, Charing Cross Hospital, London, England. This clinic is the national centre for sex re-assignment. Patients came from all regions of Great Britain.

4.2.2. Hormone Treatment

The dosage and form of hormone treatment varied somewhat from patient to patient. Patients were treated with either Premarin (conjugated equine oestrogens) or ethinyloestradiol (a synthetic oestrogen). Some patients on Premarin were also receiving Provera (medroxyprogesterone acetate, a derivative of progesterone) or Androcur (cyproterone acetate, an anti-androgen). Some patients on ethinyloestradiol were also receiving Androcur. For patients receiving Premarin, dosages ranged from 1.25 to 7.5 mgs (milligrams), daily. Dosage of Provera was 15 mgs, daily and those patients taking ethinyloestradiol received dosages ranging from 10 to 150 mcgs (micrograms), daily. Those taking Androcur received 50 to 100 mgs, daily. See Table 16 for dosage, duration and type of hormone for each patient by group. Treatment form and dosage varied because each patient's physician prescribed hormones in light of the patient's presenting clinical picture and history, as well as their physical response to hormone treatment.

Table 16: Dosage, duration and type of hormone for each patient BY group

Group	Patient	Type of hormone	Dosage	Duration (in months)
1: (Off then On)	1	ethinyloestradiol	10	3
	2	ethinyloestradiol	20	3
	3	ethinyloestradiol	50	3
	4	ethinyloestradiol	50	3
	5	ethinyloestradiol	50	3
	6	ethinyloestradiol	50	3.5
	7	ethinyloestradiol	50	3.5
	8	ethinyloestradiol	50	4
	9	ethinyloestradiol	50	4
	10	ethinyloestradiol	10	5
	11	ethinyloestradiol	50	5
	12	ethinyloestradiol	100	5
	13	ethinyloestradiol	50	6
	14	ethinyloestradiol	50	6
	15	ethinyloestradiol	50	6
	16	ethinyloestradiol	50	6
	17	ethinyloestradiol	50	6

Table 16 continued

Group	Patient	Type of hormone	Dosage	Duration (in months)
	18	ethinyloestradiol	100	6
	19	ethinyloestradiol	100	10
	20	ethinyloestradiol	10	12
	21	ethinyloestradiol	50	12
	22	ethinyloestradiol	50	12
	23	ethinyloestradiol	100	13
	24	ethinyloestradiol	50	14
	25	ethinyloestradiol	50	14
	26	ethinyloestradiol and Androcur	100 / 100	4
	27	ethinyloestradiol and Androcur	50 / 50	6
2: On then Off	1	Premarin	5	36
	2	Premarin	2	46
	3	Premarin	5	46
	4	Premarin	5	47
	5	Premarin	5	48
	6	Premarin	5	48
	7	Premarin	7.5	59
	8	Premarin	5	60
	9	Premarin	5	60

Table 16 continued

Group	Patient	Type of hormone	Dosage	Duration (in months)
	10	Premarin	7.5	60
	11	Premarin	7.5	60
	12	Premarin	7.5	70
	13	Premarin	2.5	72
	14	Premarin	7.5	72
	15	Premarin	1.25	84
	16	Premarin	7.5	96
	17	Premarin	7.5	114
	18	Premarin	7.5	120
	19	ethinyloestradiol	150	28
	20	ethinyloestradiol	100	50
	21	ethinyloestradiol	100	120
	22	ethinyloestradiol	100	120
	23	Premarin and Androcur	5 / 50	50
	24	Premarin and Androcur	7.5 / 120	72
	25	Premarin and Androcur	7.5 / 100	84
	26	Premarin and Androcur	5 / 100	100
	27	Premarin and Provera	7.5 / 15	156

Table 16 continued

Group	Patient	Type of hormone	Dosage	Duration (in months)
3: Controls	1	Premarin	5	6
1st test session	2	Premarin	2.5	7
	3	Premarin	7.5	11
	4	Premarin	1.25	12
	5	Premarin	2.5	24
	6	Premarin	7.5	24
	7	Premarin	7.5	24
	8	Premarin	7.5	29
	9	Premarin	7.5	38
	10	Premarin	7.5	39
	11	Premarin	5	42
	12	Premarin	7.5	48
	13	Premarin	5	60
	14	Premarin	7.5	70
	15	ethinyloestradiol	50	4
	16	ethinyloestradiol	100	5
	17	ethinyloestradiol	50	6
	18	ethinyloestradiol	150	24
	19	ethinyloestradiol	100	36
	20	ethinyloestradiol	50	42

Table 16 continued

Group	Patient	Type of hormone	Dosage	Duration (in months)
	21	ethinyloestradiol	150	42
	22	ethinyloestradiol	150	42
	23	ethinyloestradiol	100	44
	24	ethinyloestradiol	100	46
	25	ethinyloestradiol	100	48
	26	ethinyloestradiol	100	84
	27	ethinyloestradiol	50	88
	28	ethinyloestradiol	50	88
	29	ethinyloestradiol and Androcur	50 / 150	12
	30	ethinyloestradiol and Androcur	100 / 100	17
	31	ethinyloestradiol and Androcur	100 / 50	36
	32	ethinyloestradiol and Androcur	100 / 50	53
	33	Premarin and Androcur	5 / 50	48
	34	Premarin and Androcur	7.5 / 50	60
	35	Premarin and Provera	7.5 / 15	72
	36	Premarin and Provera	7.5 / 15	60
3: Controls	1	Premarin	7.5	26
2nd test session	2	Premarin	7.5	32

Table 16 continued

Group	Patient	Type of hormone	Dosage	Duration (in months)
	3	Premarin	7.5	33
	4	Premarin	5	48
	5	Premarin	7.5	48
	6	ethinyloestradiol	100	6
	7	ethinyloestradiol	50	12
	8	ethinyloestradiol	50	14
	9	ethinyloestradiol	150	30
	10	ethinyloestradiol	100	42
	11	ethinyloestradiol	100	46
	12	ethinyloestradiol	100	48
	13	ethinyloestradiol	150	48
	14	ethinyloestradiol	150	52
	15	ethinyloestradiol	100	84
	16	ethinyloestradiol	100	87
	17	ethinyloestradiol	50	94
	18	ethinyloestradiol and Androcur	100 / 100	20
	19	ethinyloestradiol and Androcur	50 / 150	60
	20	Premarin and Provera	7.5 / 15	71

4.2.3. Procedure

Prior to testing, written informed consent was obtained from each participant via a form approved by the local Ethics Committee (see Appendix 2). Patients were tested individually within the Gender Identity Clinic at Charing Cross Hospital. A brief, written summary outlining the aim of the study was given to each participant to read. Participants were informed that the duration of the study would be approximately one and one-half hours and they would receive payment of ten pounds at the end of the test session. Each participant received a battery of tests in the following order: The Profile Of Mood States (POMS); Handedness; Figural memory; Logical Memory; Visual PAL; Verbal PAL; Digit Span; Visual Memory Span; Judgement of Line Orientation (JOLO); FAS – word fluency; Mental Rotations; Controlled Associations; Object memory and Location memory; Vocabulary and Demographic Information.

4.2.4. Measures

1. The Profile Of Mood States (POMS) - (Lorr and McNair- 1988). The POMS was used to assess if mood at the time of testing was a confounding influence on memory or other cognitive scores. This instrument yields scores for the following bi-polar constructs: Composed / Anxious;

Agreeable / Hostile; Elated / Depressed; Confident / Unsure; Energetic / Tired; Clearheaded / Confused. Scores were obtained for each participant for each construct. Given that the scales are bi-polar, each scale score was the sum of positive item scores minus the sum of negative item scores.

2. Handedness. This was a 5 point questionnaire to assess hand preferences for writing, throwing a ball, holding a pair of scissors to cut, holding a toothbrush and drawing. For each task, the examinee circled the number that most closely describes the hand he / she prefers to use (see Appendix 3 for questionnaire used).

3. Figural memory (Wechsler Memory Scale – Revised) (WMS –R).

Participants were presented with three abstract designs, which they were to study for fifteen seconds. They were then shown nine designs, which included the designs previously shown. Participants were required to pick from the second array of designs the designs they were previously shown. There were three trials and one point was given for each correctly recalled design. To date, research has not established a sex difference on this task, but it was included as a visual memory test.

4. Logical Memory (LM) (WMS, 1945). Two brief stories were read to the participant. After each one, the participant was required to retell the story from memory. Following a delay of 30 minutes the participant was again asked to relate each story. Scores were the percentage of information recalled correctly. To date, research has not established a sex difference on this task. Although the meta-analytic findings in Chapter 3 show a negligible difference favouring males ($d = .11$), the studies reviewed were not homogenous in ES.

5. Visual PAL (WMS - R). The participant was shown a colour paired with an abstract line drawing. The participant was then required to learn the colour associated with this design. There were six colours matched with six abstract designs. The participant was then shown each of the six designs and asked to respond with the colour associated with this design. Three learning trials were given consecutively (immediate recall). A delayed recall trial was then presented following an interval of approximately 30 minutes. Each trial was scored separately, with one point given for each correctly recalled colour. To date, research has not established a sex difference on this task, but it was included as a visual analogue to the Verbal PAL memory test.

6. Verbal PAL (WMS, 1945). Participants were read a list of ten word pairs (six easy-associated pairs and four hard-associated pairs). They then were asked to supply the second word of the pair immediately after the first was given. One point was given for a correctly recalled easy pair and two points for a correctly recalled hard pair. Three learning trials were given consecutively (immediate recall) followed by a final trial after half an hour delay (delayed recall). Each trial was scored separately as a composite of the easy and hard pairs. This task shows a sex difference favouring females (Iverson, 1977; Elias, Elias, D' Agostino, Silbershtz, and Wolf, 1997). Further meta-analytic findings in Chapter 3 revealed the ES of this difference to be largest for immediate recall ($d = .30$) and negligible for PAL, delayed recall ($d = .06$).

7. Visual Reproduction (VR) (WMS). The participant was shown a simple geometric design for 10 seconds. The design was then removed and the participant was asked to draw the design as accurately as possible from memory. There were 3 separate designs and a delayed recall trial after half an hour. This task shows a sex difference favouring males (Iverson, 1993; Reite, Cullum, Stocker and Peter, 1993; Wiederholt, Cahn, Butters, Salmon, Kritz-Silverstein and Barrett-Connor, 1993; Trahan and Quintana,

1991). Meta-analytic findings from Chapter 3 support this sex difference favouring males, although ES is small ($d = .27$).

8. Digit Span (DS) (WMS – R). Participants listened to a series of number sequences, and were then asked to repeat the numbers back in the same order or in reverse. The number of digits in the sequence was increased and two trials were given for each sequence length. The examiner discontinued when the participant failed on both trials of a given sequence length. One point was given for each correctly recalled sequence. This task does not show a sex difference (Blum, Fossage and Jarvik, 1972; Kremen, Goldstein, Seidman, Toomey, Lyons, Tsuang, and Faraone, 1997; Portin, Saarijarvi, Joukamaa, and Salokangas, 1995). Meta-analytic findings from chapter 3 support the lack of sex difference on this task ($d = .01$).

9. Visual Memory Span (WMS – R). Participants were required to touch a series of coloured squares in a predetermined order, which was first demonstrated by the examiner. The number of squares touched increased. Two trials were given for each sequence length. The examiner discontinued when the participant failed on both trials of a given sequence length. One point was given for each sequence touched in the correct order. The task was then repeated with the participant instructed to touch the squares in

reverse order. To date, there are no established sex differences on this task, but it was included as a visual-spatial analogue to Digit Span. Meta-analytic findings from Chapter 3 suggests a small sex difference for this task favouring males ($d = .29$).

10. Judgement of Line Orientation (JOLO) (Collaer, 1992). Participants were required to look at two lines from an array of thirteen lines and judge the two that were in exactly the same position as two lines positioned above the array. Answers were given by indicating the numbers corresponding to the lines in the array below. This test was scored in two ways: i) One point only was given if both lines were correct (Both correct); ii) One point was given even if only one of the lines was correct and two points were given if both lines were correct (Total correct). This task shows a sex difference favouring males ($d = .85$) (Collaer and Nelson, 2002).

11. FAS – Verbal Fluency (Benton and Hamsher, 1983). Participants were asked to verbally produce within one minute as many words as possible beginning with a given letter. F, A and S are the most commonly used letters for this test, but due to the test retest nature of this study, two forms were counterbalanced (C, F, L and P, R, W). One point was given for

each correct word. This and other tests of Verbal Fluency show a sex difference favouring females (Hyde and Linn, 1988).

12. Mental Rotations (Vandenberg and Kuse, 1987). Participants were required to compare four rotated figures to a target figure and decide which two of the four figures were the same as the target figure, as opposed to mirror images. There were twelve items to complete within three minutes. One point was given when both figures in an item were correct. This and similar tasks show a sex difference favouring males (Voyer, Voyer and Bryden, 1995).

13. Controlled Associations - (Ekstrom, French and Harman, 1976). Participants were given four commonly used words and were asked to generate as many synonyms as possible. Participants had six minutes to complete the task. The number of words given was their score. This and similar tasks show a sex difference favouring females (Hines, 1990; Halpern, 1996).

14. Object memory and Location memory (Silverman and Eals, 1992). Participants studied an array of drawn objects. They were then shown another array of objects (including the original objects, with a number of

additional objects interspersed) and asked to put a cross through all the objects in the original array. For the Object memory score, one point was given for each object correctly crossed, and one point subtracted for each object incorrectly crossed. Another stimulus array was then shown, featuring the same objects in the original array. Some were in the same location and others had been moved. Participants were asked to circle the objects that were in the same place and put a cross through those that had moved. For the Location memory score, one point was given for each correct response. Both components of this task show a sex difference favouring females (Silverman and Eals, 1992).

15. Vocabulary (Ekstrom, French and Harman, 1976). The participant was told that this was a test of their knowledge of word meanings. The participant was given a target word and five other words, one of which had the same meaning or nearly the same meaning as the target word. The participant was required to mark this word. There were twenty-four target words and the participant had six minutes to complete the task. The number of words correct minus the number marked incorrectly was the score for the test. The participant was told that it would not be to their advantage to guess unless they are able to eliminate one or more of the answer choices as incorrect. This task was used as a measure of general intellectual ability.

This and other measures of Vocabulary do not show a sex difference (Hyde and Linn, 1988).

16. Demographic Information. A questionnaire was administered at the close of the test session to obtain background information about the patient, including age, sex, educational history, and duration and dosage of treatment with oestrogen or other hormones. Hormone treatment information was also verified by reference to medical records (see Appendix 4 for questionnaire).

4.2.5. Statistical analyses

MANOVA was used to analyse between and within group differences in the memory, cognitive and mood measures. This is the traditional approach used to analyse data regarding hormonal effects on behavioural outcomes and was used to aid comparability of research findings among studies in this area (Van Goozen et al, 1995; Slabbekoorn et al, 1999; Van Goozen et al, 2002). An alternative approach using multiple regression to assess the relationship between the outcome measures and the independent variables (age, vocabulary, sexuality, education, the 6 moods and hormone status) could not be used as the sample size was not large enough for the number

of predictors that would be tested. Green (1991) provides a simple rule of thumb for calculating the sample size: $N \geq 50 + 8m$ (m being the number of IVs). Using this rule, a sample size of 138 or more would be needed to employ multiple regression.

The data were analysed in 4 separate ways:

1) A between group analysis of all patients ($N = 103$) was used to determine whether previous findings in Chapter 2 could be replicated. The patients were divided into all those on hormones versus all those off hormones. To eliminate order effects, only performance at first test session was included in this analysis.

2) To reduce confounding influences of age and education on memory and cognitive performance, an additional between group analysis was performed on patients who could be matched for age and education ($n = 68$, i.e., 34 taking hormones and 34 not taking hormones).

3) 2 x 2 mixed design MANOVAs were performed on all patients who had completed two test sessions ($n = 54$), with HORMONE (on versus off) and GROUP (off then on versus on then off) as factors. This looked at groups 1

(off then on) and 2 (on then off) only, where hormone treatment was manipulated between test sessions 1 and 2. This will determine whether those taking hormone treatments performed differently to when they were not taking hormone treatment, irrespective of whether they were commencing treatment or withdrawing from treatment. Further, the interaction effects between the 2 factors (HORMONE and GROUP) allowed me to determine if any hormonal influences on memory, cognition or mood were more dramatic in those beginning treatment or those being withdrawn from treatment.

4) Groups 1 (off then on), 2 (on then off) and 3 (controls) were then analysed separately using repeated measures MANOVAs. This was to determine whether any observed changes were due to hormonal change or due to practise or boredom effects.

4.3. RESULTS

4.3.1. ANALYSIS 1: Between group differences of all patients on hormones (n = 63) versus all patients off hormones (n = 40) at first test session.

An initial analysis examined group differences in the possible confounding variables of age, mood, education, handedness, sexuality and intelligence. Vocabulary scores were used as a general indicator of intelligence. Table 17 gives descriptive statistics for these variables.

Group differences were significant for age ($F(1, 102) = 4.12, p = .045$), such that those taking hormones were older. This group was also more composed ($F(1, 102) = 11.64, p = .001$) and confident ($F(1, 102) = 6.83, p = .010$). Differences in educational background, Vocabulary, sexual orientation, handedness and the other four moods were non-significant.

Table 17: Participant characteristics for ANALYSIS 1.

Variables	Group 1 (on hormones)	Group 2 (off hormones)	F	P	ES (d)
	mean / SD	mean / SD			×
Age	39.29 / 9.56	35.45 / 9.01	4.12	.045	.41
Composed / Anxious	25.10 / 6.86	20.45 / 6.54	11.64	.001	.69
Agreeable / Hostile	29.63 / 6.13	28.65 / 6.76	.58	.447	.15
Elated / Depressed	25.63 / 7.41	23.75 / 7.54	1.56	.214	.25
Confident / Unsure	23.10 / 7.14	19.20 / 7.73	6.83	.010	.52
Energetic / Tired	20.62 / 7.40	17.98 / 10.18	2.32	.131	.30
Clearheaded / Confused	26.98 / 6.99	24.70 / 7.06	2.59	.110	.32
Sexuality †	24 / 43 / 22 / 11	28 / 48 / 15 / 9	.56	.455	
Vocabulary	4.92 / 6.43	5.55 / 7.64	.20	.654	-.09
Handedness ‡	16 / 84	15 / 85	.01	.905	
Education ††	36 / 38 / 16 / 10	15 / 48 / 23 / 14	2.66	.103	

† percentage of sample in respective sexual orientations: heterosexual / homosexual / bi-sexual / asexual

‡ percentage of sample that are left-handed / right-handed

†† percentage of sample in respective education classes: pre O' level / O' level / A' level / Degree / Post – Graduate

× ES = Effect Size (Cohen's d).

nb. For sexuality and education data were analysed using the Kruskal – Wallis test. For handedness, Chi-square was used.

Memory and cognitive measures

Data for memory and cognitive measures are in Table 18.

MANOVAs showed no significant group differences for any of the cognitive measures, suggesting that transsexual patients on and off hormones performed similarly on these tasks.

Table 18: Performance on the memory and cognitive measures for

ANALYSIS 1.

Measure	Group 1 (on hormones) mean / SD	Group 2 (off hormones) mean / SD	F	P / ES (d)
Mental Rotation	3.01 / 2.12	3.20 / 2.54	.17	.684 / -.08
JOLO – Both correct	10.72 / 5.08	9.93 / 3.89	.71	.401 / .18
JOLO – Total correct	28.13 / 6.70	27.05 / 6.82	.62	.433 / .16
FAS	37.27 / 11.90	38.75 / 11.41	.39	.533 / -.13
Controlled Associations	13.26 / 6.68	15.25 / 8.22	1.81	.182 / -.26
Verbal PAL, trial 1	6.34 / 1.76	6.38 / 2.47	.00	.951 / -.02
Verbal PAL, trial 2	7.95 / 1.63	7.90 / 2.07	.02	.887 / .02
Verbal PAL, trial 3	8.69 / 1.56	8.65 / 1.81	.02	.886 / .02
Verbal PAL (delayed recall)	8.32 / 1.89	8.50 / 1.80	.24	.628 / -.10
First and Last names	3.68 / 3.30	4.23 / 3.57	.63	.428 / -.16
Visual PAL, trial 1	2.87 / 1.71	3.13 / 2.09	.45	.505 / -.14
Visual PAL, trial 2	4.14 / 1.65	4.00 / 1.96	.16	.692 / .08
Visual PAL, trial 3	4.71 / 1.54	4.55 / 1.90	.23	.632 / .09

Table 18 continued

Measure	Group 1 (on hormones) mean / SD	Group 2 (off hormones) mean / SD	F	P / ES (d)
Visual PAL, (immediate recall)	11.77 / 4.04	11.68 / 5.36	.01	.912 / .02
Visual PAL--(delayed recall)	4.56 / 1.55	4.65 / 1.64	.09	.769 / -.06
Object memory	13.63 / 4.66	13.53 / 5.22	.01	.916 / .02
Location memory	14.85 / 5.83	14.23 / 5.74	.29	.592 / .11
DS Forwards	7.74 / 2.16	7.57 / 2.46	.14	.712 / .07
DS Backwards	6.43 / 2.10	6.15 / 2.55	.36	.548 / .12
DS Total	14.14 / 3.58	13.73 / 4.45	.28	.601 / .10
Visual Span Forwards	8.06 / 1.60	8.07 / 2.61	.00	.980 / -.00
Visual Span Backwards	7.74 / 2.07	7.40 / 2.19	.64	.427 / .16
Visual Span Total	15.81 / 3.17	15.48 / 4.24	.21	.652 / .09
LM (immediate recall)	39.02 / 12.98	41.79 / 18.94	.78	.380 / -.17
LM (delayed recall)	32.71 / 14.82	35.88 / 18.52	.92	.340 / -.19
VR (immediate recall)	17.52 / 3.36	17.28 / 3.92	.12	.732 / .07
VR (delayed recall)	15.22 / 4.27	15.70 / 4.22	.31	.579 / -.11
Figural memory	6.82 / 1.36	6.92 / 1.63	.11	.739 / -.07

Analyses of Covariance

Patients treated with oestrogen were older and more composed and confident than patients awaiting treatment. To examine the possibility that differences between groups in age, composure and confidence were distorting results, several analyses of covariance were conducted. The main criterion for a covariate analysis is a 'substantial linear correlation with the dependent variable' (Keppel, 1991). Where age or mood correlated with the dependent variable at the $p < .05$ level, ANCOVAs were performed on the data. Age correlated positively with Vocabulary scores ($r = .22$, $p = .027$), such that the older the patients the higher they scored on this task. Conversely, age correlated negatively with Visual PAL, trial 2, ($r = -.21$, $p = .037$) with the composite score for Visual PAL, trials 1-3 (immediate recall) ($r = -.21$, $p = .030$) and with Visual PAL, trial 4 (delayed recall) ($r = -.22$, $p = .029$), such that the lower the age of patients the higher they scored. Composed correlated positively with Visual PAL, trial 3 ($r = .20$, $p = .041$), such that the more composed the patients, the higher their score. For this reason, data was reanalysed for these dependent variables using age, and this mood (composed) as covariates. There were no significant

differences in memory or cognitive performance between patients on versus off oestrogen treatment.

Of further interest was whether Vocabulary scores (used as a measure of general intellectual ability) were distorting results. Vocabulary scores correlated positively with the majority of memory and cognitive scores, such that the higher the Vocabulary score the higher patients' scores on the following measures: First and Last names ($r = .34, p = .001$); DS Forwards ($r = .44, p = .001$); DS Backwards ($r = .41, p = .001$); DS Total ($r = .50, p = .001$); Visual Span Forwards ($r = .40, p = .001$); Visual Span Backwards ($r = .37, p = .001$); Visual Span Total ($r = .45, p = .001$); Verbal PAL, trial 1 ($r = .47, p = .000$); Verbal PAL, trial 2 ($r = .34, p = .001$); Verbal PAL, trial 3 ($r = .34, p = .000$); Verbal PAL, trial 4 (delayed recall) ($r = .38, p = .001$); Visual PAL, trial 2 ($r = .23, p = .021$); Visual PAL, trials 1-3 (immediate recall) ($r = .21, p = .032$); Controlled Associations ($r = .61, p = .000$); Object memory ($r = .24, p = .016$); JOLO (Both correct) ($r = .37, p = .001$); JOLO (Total correct) ($r = .40, p = .001$); FAS ($r = .42, p = .001$); VR (immediate recall) ($r = .28, p = .004$); VR (delayed recall) ($r = .33, p = .001$); LM (immediate recall) ($r = .44, p = .001$); LM (delayed recall) ($r = .38, p = .001$). For this reason data were reanalysed for these dependent variables using Vocabulary as a covariate. Results of the ANCOVA

indicated that there were no significant differences between those taking hormones and those not taking hormones on any of the memory or cognitive measures.

Duration of Treatment

In Chapter 2 no relationship was found between the length of time patients had been taking hormone treatment and their scores on the memory and cognitive tasks. It was of interest to examine whether this finding was consistent in this sample. Duration of treatment for participants in this sample ranged from 4 months to 156 months. Within the oestrogen-treated group, no significant correlations were found between duration of treatment, in months, and performance on any of the memory or cognitive measures. Similarly, all correlations between duration and mood measures were non-significant, although all were in a negative direction.

Dosage of Treatment

As with Chapter 2, it was important to examine whether dosage of hormone treatment correlated with memory, cognitive or mood measures. Using the conversion formula of Premarin dosage to ethinyloestradiol dosage to

create a standardised unit ⁹ a positive correlation was found between dosage and JOLO (Both correct) ($r = .27$, $p = .030$) and JOLO (Total correct) ($r = .27$, $p = .032$), suggesting that the higher the dosage of treatment the higher the patients' score on this task. None of the correlations for the other measures were significant, although all correlations of the 6 moods with dosage were in a positive direction.

Treatment with Different Hormone Combinations

As 13 patients were taking combinations of oestrogens with either Androcur (Androcur with ethinyloestradiol = 4; Androcur with Premarin = 6) or Progesterone (Premarin with Provera = 3), it was reasonable to hypothesise that these additional hormones may influence the effects of oestrogen on memory, cognitive or mood measures. Therefore patients taking oestrogen only were analysed separately ($n = 50$).

⁹ 50 micrograms of ethinyloestradiol equates approximately to 5 mg of Premarin (Goodman and Gilman, 1985)

Table 19: Participant characteristics (n = 50, on oestrogen / n = 40, off hormone treatment).

Variables	Group 1 (on hormones) mean /SD	Group 2 (off hormones) mean /SD	F	P	ES (d)
Age	40.56 / 9.62	35.45 / 9.01	6.63	.012	.55
Composed / Anxious	26.20 / 6.90	20.45 / 6.54	16.18	.000	.86
Agreeable / Hostile	30.54 / 4.85	28.65 / 6.77	2.39	.127	.33
Elated / Depressed	26.06 / 7.42	23.75 / 7.54	2.12	.149	.31
Confident / Unsure	23.94 / 7.25	19.20 / 7.73	8.96	.004	.63
Energetic / Tired	20.62 / 7.40	17.98 / 10.18	3.39	.069	.39
Clearheaded / Confused	27.88 / 6.50	24.70 / 7.06	4.95	.029	.34
Sexuality †	24 / 36 / 28 / 12	28 / 47 / 15 / 10	1.14	.285	
Vocabulary	4.98 / 6.61	5.55 / 7.64	.14	.705	-.08
Handedness ‡	16 / 84	15 / 85	.02	.897	
Education ‡‡	34 / 36 / 18 / 8 / 4	15 / 47 / 23 / 12 / 3	2.35	.125	

† percentage of sample in respective sexual orientations: heterosexual / homosexual / bi-sexual / asexual

‡ percentage of sample that are left-handed / right handed

‡‡ percentage of sample in respective education classes: pre O' level / O' level / A' level / Degree / Post - Graduate

nb. For sexuality and education data were analysed using the Kruskal – Wallis test. For handedness, Chi-square was used.

When analysing those on oestrogen alone versus those off hormone therapy, those taking oestrogen remained older ($F(1, 89) = 6.63, p = .012$), more composed ($F(1, 89) = 16.18, p = .001$) and more confident ($F(1, 89) = 8.96, p = .004$). Effect sizes were larger than those in Analysis 1. Furthermore a between group difference was also detected on Clearheaded / Confused ($F(1, 89) = 4.95, p = .029$), such that those on oestrogen were more clearheaded. There was also borderline significance favouring those taking hormones on Energetic / Tired ($F(1, 89) = 3.39, p = .069$). Non-significant differences did not alter from the previous analysis on sexuality, education, handedness or Vocabulary.

Data for memory and cognitive measures for this subgroup of 90 patients are in Table 20.

Table 20: Performance on the memory and cognitive measures**(oestrogen only versus those off hormone treatment).**

Measure	Group 1 (on hormones) mean / SD	Group 2 (off hormones) mean / SD	F	P / ES (d)
Mental Rotation	3.06 / 2.19	3.20 / 2.54	.09	.772 / -.06
JOLO – Both correct	10.57 / 4.96	9.93 / 3.89	.45	.504 / .14
JOLO – Total correct	28.11 / 5.62	27.05 / 6.82	.65	.423 / .45
FAS	37.12 / 12.48	38.75 / 11.41	.41	.524 / -.14
Controlled Associations	12.51 / 6.72	15.25 / 8.22	3.03	.086 / -.37
Verbal PAL, trial 1	6.28 / 1.77	6.38 / 2.47	.05	.833 / -.05
Verbal PAL, trial 2	7.86 / 1.67	7.90 / 2.07	.01	.919 / -.02
Verbal PAL, trial 3	8.66 / 1.62	8.65 / 1.81	.00	.978 / .01
Verbal PAL (delayed recall)	8.30 / 1.90	8.50 / 1.80	.26	.612 / -.01
First and Last names	3.58 / 3.34	4.23 / 3.57	.79	.376 / -.02
Visual PAL, trial 1	2.90 / 1.74	3.13 / 2.09	.31	.579 / -.11
Visual PAL, trial 2	4.04 / 1.64	4.00 / 1.96	.01	.916 / .02
Visual PAL, trial 3	4.70 / 1.57	4.55 / 1.90	.17	.683 / .09
Visual PAL (immediate recall)	11.70 / 4.20	11.68 / 5.36	.00	.980 / .00
Visual PAL (delayed recall)	4.50 / 1.56	4.65 / 1.64	.20	.658 / -.09
Object memory	13.47 / 4.53	13.53 / 5.22	.00	.959 / -.01
Location memory	14.64 / 5.56	14.23 / 5.74	.12	.732 / .07
DS Forwards	7.70 / 2.13	7.57 / 2.46	.07	.797 / .06
DS Backwards	6.34 / 2.07	6.15 / 2.55	.16	.698 / .08
DS Total	14.00 / 3.52	13.73 / 4.45	.11	.749 / .07
Visual Span Forwards	8.08 / 1.61	8.07 / 2.61	.00	.989 / .00
Visual Span Backwards	7.69 / 1.97	7.40 / 2.19	.45	.504 / .14
Visual Span Total	15.78 / 3.06	15.48 / 4.24	.16	.697 / .08
LM (immediate recall)	37.92 / 11.72	41.79 / 18.94	1.41	.238 / -.25

Table 20 continued

Measure	Group 1 (on hormones) mean / SD	Group 2 (off hormones) mean / SD	F	P / ES (d)
LM (delayed recall)	31.67 / 13.94	35.88 / 18.52	1.52	.221 / -.26
VR (immediate recall)	17.31 / 3.37	17.28 / 3.92	.00	.963 / .00
VR (delayed recall)	15.24 / 4.05	15.70 / 4.22	.28	.600 / -.11
Figural memory	6.90 / 1.42	6.92 / 1.63	.00	.938 / -.01

There were no significant differences between patients in the oestrogen only group compared to the untreated group. These results are similar to those in the former analysis.

Analyses of Covariance

Correlational statistics were again used to examine whether there was an association of age, Composed / Anxious, Confident / Unsure and Clearheaded / Confused and Vocabulary scores with memory and cognitive scores. Age correlated positively with Vocabulary scores ($r = .24$, $p = .021$), such that the older the patient, the higher their Vocabulary score. However, age correlated negatively with Visual PAL, trial 4 (delayed recall) ($r = -.22$, $p = .03$), such that the lower their age the higher they scored on this task. Composed / Anxious correlated with Visual Span Backwards ($r = .31$, $p = .003$), Visual PAL, trial 3 ($r = .24$, $p = .025$), the

composite score for Visual PAL, trials 1-3 (immediate recall) ($r = .21, p = .051$), JOLO (Total score) ($r = .21, p = .052$) and LM (immediate recall) ($r = .23, p = .033$). Confident / Unsure correlated with Visual PAL, trial 2 ($r = .21, p = .045$), JOLO (Both correct) ($r = .25, p = .018$) and JOLO (Total correct) ($r = .29, p = .006$). Clearheaded / Confused did not significantly correlate with any memory or cognitive measure. All correlations of these dependent variables with mood measures were positive, such that the more positive the mood, the higher patients scored. Vocabulary scores correlated positively with the majority of memory and cognitive scores, such that the higher the Vocabulary score the higher patients' scores on the following measures: First and Last names ($r = .34, p = .001$); DS Forwards ($r = .43, p = .001$); DS Backwards ($r = .39, p = .001$); DS Total ($r = .48, p = .001$); Visual Span Forwards ($r = .42, p = .001$); Visual Span Backwards ($r = .39, p = .001$); Visual Span Total ($r = .42, p = .001$); Verbal PAL, trial 1 ($r = .38, p = .001$); Verbal PAL, trial 2 ($r = .24, p = .020$); Verbal PAL, trial 3 (immediate recall) ($r = .22, p = .035$); Verbal PAL, trial 4 (delayed recall) ($r = .21, p = .051$); Controlled Associations ($r = .66, p = .001$); Object memory ($r = .23, p = .026$); Location memory ($r = .36, p = .001$); JOLO (Both correct) ($r = .36, p = .001$); JOLO (Total correct) ($r = .45, p = .001$); FAS ($r = .45, p = .001$); VR (immediate recall) ($r = .27, p = .011$); VR (delayed recall) ($r = .32, p = .002$); LM (immediate recall) ($r = .45, p =$

.001); LM (delayed recall) ($r = .366$, $p = .001$). When age, these moods (Composed / Anxious and Confident / Unsure) and Vocabulary were used as covariates non-significant group differences remained non-significant.

Duration of Treatment

Length of treatment correlated positively with Visual Span Backwards ($r = .32$, $p = .022$) and JOLO (Total correct) ($r = .34$, $p = .016$), respectively. No correlations between mood measures and duration were significant in the negative direction.

Dosage of treatment

Dosage of treatment correlated positively with Digit Span Backwards ($r = .35$, $p = .012$), JOLO (Total correct) ($r = .31$, $p = .031$), JOLO (Both correct) ($r = .28$, $p = .053$) and LM (delayed recall) ($r = .28$, $p = .051$). There were no significant correlations between mood and dosage of treatment, although all were in a positive direction.

Does additional Provera or Androcur influence mood?

Further analyses explored whether combinations of oestrogen with either Androcur or Provera influenced the magnitude of the difference between those taking hormones and those not, in the mood measures. To examine whether the addition of Provera to oestrogen influenced results, those taking oestrogen with Androcur were excluded from this analysis ($n = 10$). Group differences in three moods remained: Composed / Anxious ($F(1, 92) = 14.65, p = .001$); Confident / Unsure ($F(1, 92) = 8.14, p = .005$) and Clearheaded / Confused ($F(1, 92) = 4.24, p = .042$). Group differences did not remain in Energetic / Tired. Effect sizes were similar to those for the whole sample.

To examine whether the addition of Androcur to oestrogen influenced results, those taking Provera in addition to oestrogen were excluded ($n = 3$). Between group differences favouring those taking hormones remained significant for Composed / Anxious ($F(1, 99) = 2.61, p = .001$) and Confident / Unsure ($F(1, 99) = 7.41, p = .008$). Group differences were not detected in Clearheaded / Confused and Energetic / Tired, however.

Analyses of Covariance

For these analyses excluding oestrogen with either Androcur or Provera, correlations between age, Composed / Anxious, Clearheaded / Confused, Confident / Unsure, Vocabulary and the memory and cognitive measures were explored. As with the previous analysis, where there were significant associations ($p < .05$) data were reanalysed with these as covariates. Similar to previously found, between group differences remained non-significant.

4.3.2. ANALYSIS 2: Matched group differences of all patients on hormones versus all patients off hormones.

As it is difficult with the design used in Analysis 1 to rule out subject variables such as age and education as influencing the outcome of results, further analyses matched subjects on these variables. This reduced the sample to 34 participants in each group.

Group differences were examined on the remaining potentially confounding variables of mood, handedness, sexuality and intelligence.

Table 21 gives descriptive statistics for these variables.

With group differences in age and education minimised, group differences paralleled those found in Analysis 1. Those taking hormones were more composed ($F(1, 67) = 5.12, p = .027$) and confident ($F(1, 67) = 6.53, p = .013$). Differences in sexual orientation, handedness, Vocabulary and the other 4 moods were not significant.

Table 21: Participant characteristics for ANALYSIS 2.

Variables	Group 1 (on hormones)	Group 2 (off hormones)	F	P	ES (d)
	mean / SD	mean / SD			
Age	37.68 / 7.77	36.88 / 8.02	.17	.680	.10
Composed / Anxious	24.56 / 7.01	20.76 / 6.81	5.12	.027	.55
Agreeable / Hostile	29.38 / 7.26	29.18 / 7.03	.01	.910	.03
Elated / Depressed	26.41 / 7.62	23.79 / 7.52	2.04	.158	.35
Confident / Unsure	23.71 / 7.05	19.09 / 7.83	6.53	.013	.62
Energetic / Tired	21.38 / 7.35	18.26 / 10.67	1.97	.165	.35
Clearheaded / Confused	26.21 / 7.83	24.29 / 7.45	1.06	.306	.25
Sexuality †	24 / 43 / 22 / 11	28 / 48 / 15 / 9	.56	.455	
Vocabulary	5.59 / 5.92	4.91 / 7.41	.16	.692	.10
Handedness ‡	84 / 16	85 / 15	.00	1.000	
Education ‡‡	36 / 38 / 16 / 10	15 / 48 / 23 / 14	.05	.824	

† percentage of sample in respective sexual orientations: heterosexual / homosexual / bisexual / asexual

‡ percentage of sample that are left-handed / right handed

‡‡ percentage of sample in respective education classes: pre O' level / O' level / A' level / Degree / Post - Graduate

nb. For sexuality and education data were analysed using the Kruskal – Wallis test. For handedness, Chi-square was used.

Memory and cognitive measures

Data for memory and cognitive measures are in Table 22.

Table 22: Performance on the memory and cognitive measures for ANALYSIS 2.

Measure	Group 1 (on hormones) mean / SD	Group 2 (off hormones) mean / SD	F	P / ES (d)
Mental Rotation	3.24 / 1.97	3.18 / 2.62	.01	.925 / .03
JOLO – Both correct	11.82 / 5.40	9.97 / 3.73	2.71	.104 / .40
JOLO – Total correct	29.79 / 4.94	26.79 / 7.01	4.16	.045 / .50
FAS	37.59 / 11.44	37.50 / 11.11	.00	.974 / .00
Controlled Associations	13.77 / 6.47	14.38 / 6.80	.14	.706 / -.09
Verbal PAL, trial 1	6.59 / 1.74	6.21 / 2.53	.53	.471 / .18
Verbal PAL, trial 2	8.12 / 1.45	7.90 / 2.07	.37	.546 / .13
Verbal PAL, trial 3	8.79 / 1.32	8.68 / 1.80	.09	.760 / .07
Verbal PAL (delayed recall)	8.50 / 1.64	8.53 / 1.66	.01	.942 / -.02
First and Last names	4.02 / 3.50	4.12 / 3.48	.01	.909 / -.03
Visual PAL, trial 1	3.32 / 1.85	3.03 / 2.04	.39	.536 / .15
Visual PAL, trial 2	4.44 / 1.46	3.85 / 1.97	1.95	.167 / .35
Visual PAL, trial 3	4.79 / 1.43	4.53 / 1.89	.42	.518 / .16
Visual PAL3 (immediate recall)	12.56 / 3.88	11.41 / 5.23	1.06	.308 / .25
Visual PAL (delayed recall)	4.74 / 1.50	4.59 / 1.60	.16	.688 / .10
Object memory	14.62 / 3.95	14.09 / 5.06	.23	.632 / .12
Location memory	15.35 / 4.83	14.29 / 5.83	.67	.426 / .20
DS Forwards	7.74 / 2.19	7.44 / 2.48	.27	.606 / .13
DS Backwards	6.62 / 2.31	6.29 / 2.70	.28	.597 / .13

Table 22 continued

Measure	Group 1 (on hormones) mean / SD	Group 2 (off hormones) mean / SD	F	P / ES (d)
DS Total	14.29 / 3.84	13.74 / 4.67	.29	.592 / .24
Visual Span Forwards	8.18 / 1.70	7.91 / 2.73	.23	.633 / .12
Visual Span Backwards	7.88 / 1.67	7.26 / 2.31	1.60	.211 / .31
Visual Span Total	16.06 / 2.77	15.18 / 4.49	1.60	.211 / .24
LM (immediate recall)	40.98 / 14.31	42.40 / 19.12	.12	.730 / -.08
LM (delayed recall)	34.17 / 14.99	36.41 / 19.43	.28	.596 / -.13
VR (immediate recall)	17.65 / 3.60	17.37 / 3.96	.07	.788 / .07
VR (delayed recall)	15.32 / 4.41	15.68 / 4.33	.79	.378 / -.08
Figural memory	6.74 / 1.38	6.92 / 1.56	.24	.623 / -.12

MANOVAS paralleled the findings of Analysis 1, with exception of JOLO (Total correct) where those on hormones scored higher than those not taking hormones ($F(1, 67) = 4.16, p = .045$). All other memory and cognitive scores did not differ significantly.

Analyses of Covariance

As with Analysis 1, the between group differences in composure and confidence were examined as possible influences on memory and cognitive measures. Several analyses of covariance were conducted following the same statistical criterion as Analysis 1 (Keppel, 1991).

Where significant correlations were found between two measures, all were in a positive direction, such that the more positive the mood of the patients, the higher they scored on the tasks. Also, age correlated positively with Vocabulary scores, ($r = .28$, $p = .023$) such that the higher the age, the higher the Vocabulary scores. Age correlated negatively with Visual PAL, trial 3 ($r = -.31$, $p = .010$) and the composite score for Visual PAL, trials 1-3 (immediate recall) ($r = -.27$, $p = .025$). The lower their age the higher participants scored on this task. The mood, Composed / Anxious, correlated positively with Object memory ($r = .31$, $p = .010$), Location memory ($r = .29$, $p = .015$), Visual PAL, trial 2 ($r = .28$, $p = .021$), Visual PAL, trial 3 ($r = .31$, $p = .010$) and the composite score for Visual PAL, trials 1-3 (immediate recall) ($r = .29$, $p = .015$). The mood, Confident / Unsure, correlated positively with Visual PAL, trial 2 ($r = .26$, $p = .035$), the composite score for Visual PAL, trials 1-3 (immediate recall) ($r = .25$, $p = .044$), Object memory ($r = .26$, $p = .035$), Location memory ($r = .24$, $p = .049$), JOLO (Both correct) ($r = .24$, $p = .052$), JOLO (Total correct) ($r = .27$, $p = .025$) and VR (immediate recall) ($r = .27$, $p = .029$) and VR (delayed recall) ($r = .23$, $p = .051$). When the two moods were used as covariates, JOLO (Total correct) no longer differed significantly for hormone treated versus non-treated patients. Vocabulary scores correlated positively with the majority of memory and cognitive scores, such that the higher the

Vocabulary score the higher patients' scores on the following measures: First and Last names ($r = .28, p = .020$); DS Forwards ($r = .51, p = .001$); DS Backwards ($r = .45, p = .001$); Visual Span Backwards ($r = .48, p = .001$); Visual Span Total ($r = .45, p = .001$); Verbal PAL, trial 1 ($r = .47, p = .001$); Verbal PAL, trial 1 ($r = .48, p = .001$); Verbal PAL, trial 2 ($r = .30, p = .011$); Verbal PAL, trial 3 ($r = .31, p = .011$); Verbal PAL, trial 4 (delayed recall) ($r = .34, p = .005$); Controlled Associations ($r = .55, p = .000$); Object memory ($r = .33, p = .005$); Location memory ($r = .29, p = .016$); FAS ($r = .42, p = .001$); JOLO (Both correct) ($r = .31, p = .010$); JOLO (Total correct) ($r = .39, p = .001$); FAS ($r = .42, p = .001$); VR (immediate recall) ($r = .35, p = .004$); VR (delayed recall) ($r = .33, p = .006$); LM (immediate recall) ($r = .441, p = .001$); LM (delayed recall) ($r = .349, p = .004$). For this reason data were reanalysed for these dependent variables using Vocabulary as a covariate. Results of the ANCOVA indicated that there were no significant differences between those taking hormones and those not taking hormones on any of the memory or cognitive measures.

Duration of Treatment

In this sample, duration of treatment ranged from 4 months to 156 months.

Within the oestrogen treated group, correlations between duration of treatment, in months, and memory, cognitive and mood measures were non-significant, with the exception of Object memory ($r = -.42$, $p = -.041$).

The shorter time patients had been on treatment the higher their score on this task. Associations between duration of treatment and mood were not significant.

Dosage of Treatment

No correlations between dosage of oestrogen and memory, cognitive or mood scores, were significant.

4.3.3. ANALYSIS 3: A 2 x 2 mixed design for patients who had completed both test sessions.

This analysis collapsed group 1 (off then on) and group 2 (on then off) in a 2 x 2 mixed design for patients who had completed both test sessions. This allowed me to examine whether patients taking hormones differed from when they were not taking hormones in mood, memory and cognition, irrespective of whether they had just begun hormones (group 1) or whether they had been taking hormones for a longer period (group 2) (HORMONE - within subjects factor). This design also examined whether groups 1 and 2 differed in results obtained on mood, memory and cognition i.e. administration versus withdrawal of hormones (GROUP - between subjects factor). This analysis attempted to answer 2 questions: i) Does performance alter as a result of hormone status? (on versus off); ii) If there is a change in performance is the change more dramatic as a result of short-term administration or withdrawal from long-term treatment?

Table 23: Participant characteristics with between group factor HORMONE (OFF vs. ON – n= 54) and within group factor GROUP (OFF then ON vs ON then OFF – n = 54).

Variables	Hormone status		Group		Hormone		Group X Hormone		ES (d) δ
	Group 1 (Time 1) + Group 2 (Time 2) (mean / SD) OFF hormones	Group 1 (Time 2) + Group 2 (Time 1) (mean / SD) ON hormones	F	P	F	P	F	P	
	Age	38.70 / 9.35	38.19 / 10.72	1.81	.184	.63	.430	.12	
Composed / Anxious	22.07 / 6.74	24.37 / 7.09	.25	.621	6.19	.016	3.41	.071	.49
Agreeable / Hostile	30.39 / 6.51	29.87 / 5.35	.00	.957	.34	.565	.68	.436	-.12
Elated / Depressed	25.17 / 7.11	25.00 / 7.37	1.20	.278	.03	.873	.04	.845	-.02
Confident / Unsure	20.78 / 7.72	22.44 / 7.11	.74	.393	2.00	.163	2.47	.122	.33
Energetic / Tired	19.00 / 9.85	19.87 / 7.62	.40	.529	.35	.560	.38	.543	.14

Table 23 continued

	Hormone Status		Group		Hormone		Group X		ES (d) δ
	Group 1 (Time 1) + Group 2 (Time 2) (mean / SD) OFF hormones	Group 1 (Time 2) + Group 2 (Time 1) (mean / SD) ON hormones	F	P	F	P	F	P	
Clearheaded / Confused	25.56 / 5.93	26.24 / 6.38	2.74	.104	.64	.428	.21	.652	.16
Sexuality †	18.5 / 53.7 / 20.4 / 7.4	20.4 / 53.7 / 18.5 / 7.4	2.20	.451					
Vocabulary	5.52 / 7.14	5.94 / 7.01	.25	.618	.37	.548	.75	.389	.11
Handedness ‡	85.2 / 14.8	85.2 / 14.8	2.50	.287					
Education ††	18.5 / 44.4 / 18.5 / 16.7 / 1.9	24.1 / 42.6 / 20.4 / 9.3 / 3.7	.145	.703					

† percentage of sample in respective sexual orientations: heterosexual / homosexual / bi-sexual / asexual (GROUP FACTOR) – Kruskal-Wallis test used.

‡ percentage of sample that are left-handed / right handed (GROUP FACTOR) – Chi – Square test used.

†† percentage of sample in respective education classes: pre O' level / O' level / A' level / Degree / Post – Graduate (GROUP FACTOR)

δ ES computed for the repeated measures HORMONE FACTOR, using the correlation of the scores between time 1 and time 2 (Cohen. 1988).
nb. For sexuality, education and handedness these variables remain constant (HORMONE FACTOR).

Table 24: Performance on memory and cognitive tasks with between group factor, HORMONE (OFF vs. ON) and within group factor, GROUP (OFF then ON vs ON then OFF)

Measure	Hormone status		Group		Hormone		Group X Hormone		ES δ
	OFF (Mean / SD)	ON (Mean / SD)	F	P	F	P	F	P	
Mental Rotation	3.15 / 2.40	3.39 / 2.51	.47	.495	.44	.509	.44	.509	.13
JOLO – Both correct	10.13 / 4.07	10.87 / 5.33	.05	.827	1.67	.201	.60	.442	.16
JOLO – Total correct	27.57 / 6.53	28.30 / 6.36	.19	.669	1.39	.244	.21	.649	.20
FAS	38.39 / 13.18	38.66 / 11.89	.09	.769	.04	.835	2.06	.157	.04
Controlled Associations	14.46 / 7.43	13.63 / 6.51	.03	.876	1.26	.267	.60	.443	-.02
Verbal PAL, trial 1	6.54 / 2.21	6.61 / 2.11	.02	.882	.05	.822	.32	.573	.04
Verbal PAL, trial 2	8.04 / 1.87	8.09 / 2.06	.01	.910	.06	.807	.17	.685	.05
Verbal PAL, trial 3	8.67 / 1.63	8.67 / 1.64	.23	.637	.00	1.000	.26	.615	.16
Verbal PAL (delayed recall)	8.43 / 1.81	8.32 / 1.93	1.28	.263	.25	.618	1.37	.247	-.10

Table 24 continued

	Hormone status		Group		Hormone		Group X Hormone		ES δ
	OFF (Mean / SD)	ON (Mean / SD)	F	P	F	P	F	P	
First and Last names	4.48 / 3.72	4.02 / 3.70	.08	.776	2.26	.139	1.30	.259	-.27
Visual PAL, trial 1	3.74 / 2.00	3.17 / 1.84	.04	.843	4.45	.040	3.46	.069	-.36
Visual PAL, trial 2	4.33 / 1.86	4.28 / 1.63	.14	.709	.06	.808	2.98	.090	-.05
Visual PAL, trial 3	4.78 / 1.88	4.79 / 1.59	.58	.449	.00	.949	1.45	.234	.00
Visual PAL (immediate recall)	12.75 / 5.12	12.25 / 4.34	.14	.706	.92	.343	3.69	.060	-.19
Visual PAL (delayed recall)	4.94 / 1.94	4.53 / 1.68	.44	.511	2.39	.128	1.27	.264	-.31
Object memory	13.26 / 4.99	13.63 / 4.69	.98	.327	.31	.581	4.94	.031	.11
Location memory	14.67 / 6.00	15.83 / 5.66	1.53	.222	1.53	.222	.59	.448	-.07
DS Forwards	7.61 / 2.15	7.80 / 2.24	.07	.792	.67	.417	.03	.871	.17
DS Backwards	5.98 / 2.19	6.67 / 2.31	.01	.923	8.26	.006	.01	.938	.57
DS Total	13.59 / 3.72	14.46 / 4.24	.04	.845	6.08	.017	.01	.958	.49

Table 24 continued

	Hormone status		Group		Hormone		Group X Hormone		ES δ
	OFF (Mean / SD)	ON (Mean / SD)	F	P	F	P	F	P	
	Visual Span Forwards	8.02 / 2.28	8.02 / 1.98	.01	.943	.00	1.000	1.19	
Visual Span Backwards	7.43 / 2.09	7.91 / 2.08	.01	.941	2.98	.090	1.13	.293	.32
Visual Span Total	15.44 / 3.69	15.93 / 3.53	.00	1.00	1.36	.250	2.05	.158	.60
LM (immediate recall)	43.94 / 17.27	44.71 / 16.89	1.63	.207	.13	.719	2.00	.164	.08
LM (delayed recall)	37.81 / 17.24	37.13 / 17.16	4.66	.036	.13	.721	2.18	.145	.00
VR (immediate recall)	17.19 / 4.09	17.39 / 3.41	.02	.898	.27	.605	.27	.605	.08
VR (delayed recall)	15.55 / 4.73	16.05 / 4.01	.91	.345	1.29	.261	1.29	.261	.17
Figural memory	7.19 / 1.64	7.00 / 1.63	.00	1.000	.97	.330	.97	.330	-.17

δ ES computed for the repeated measures HORMONE factor, using the correlation of the scores between time 1 and time 2 (Cohen, 1988).

Participant characteristics for ANALYSIS 3.

Unlike Analyses 1 and 2, patients taking hormones were not significantly older than those not taking hormones, however findings were replicated between group differences in Analyses 1 and 2 for composure ($F(1, 52) = 6.19, p = .016$). Patients taking hormones were more composed than when they were not taking hormones. There was an interaction effect that approached significance ($F(1, 52) = 3.41, p = .071$) of GROUP x HORMONE. Analysis 4 examines this interaction.

Memory measures

Data for memory and cognitive measures are presented in Table 24.

There was a main effect of HORMONE for DS Backwards ($F(1, 52) = 8.26, p = .006$), DS Total scores ($F(1, 52) = 6.08, p = .017$) and Visual PAL, trial 1 ($F(1, 52) = 4.42, p = .040$). Patients performed better on DS when taking hormones compared to when they were not taking hormones, whereas when patients were not taking hormones they performed better than when taking hormones on the Visual PAL, trial 1. There was a significant GROUP difference on LM (delayed recall) ($F(1, 52) = 4.66, p = .036$), such that those in group 1 (off then on) scored higher on this

measure than those in group 2 (on then off) (see Figure 8). There was a significant interaction effect of GROUP x HORMONE for Object memory ($F(1, 52) = 4.94, p = .03$). Figure 9 shows that group 2 performed worse on this task when withdrawn from hormones than when they were taking hormones. In contrast, the performance of those in group 1 remained roughly the same when taking and not taking hormones.

There also was a significant interaction for Visual PAL, trial 1 ($F(1, 52) = 4.94, p = .03$) and a borderline significant interaction for the composite score for Visual PAL, trials 1-3 (immediate recall) ($F(1, 52) = 3.69, p = .06$). For Visual PAL, trial 1, scores in group 1 were similar whether taking hormones or not. For group 2, when these patients were withdrawn from treatment their performance improved (see Figure 10). For the composite score of Visual PAL, trials 1-3 (immediate recall), this pattern was the same, with no change in performance in group 1, but an improvement in group 2 when withdrawn from hormones (see Figure 11).

ANALYSIS 4 will explore these interpretations of interaction effects in more detail giving Means, SDs, significance levels and ESs for groups 1 and 2 separately. There were no other significant main or interaction effects found on the other memory tasks ((Verbal PAL, First and Last names,

Visual PAL, trial 2 and Visual PAL, trial 4 (delayed recall), Location memory, DS Forwards, Visual Span, LM (immediate recall), VR and Figural memory)).

Cognitive measures

There were no significant main or interaction effects for any of the cognitive measures (Mental Rotations, JOLO, FAS and Controlled Associations). See Table 24 for individual test results.

Analyses of Covariance

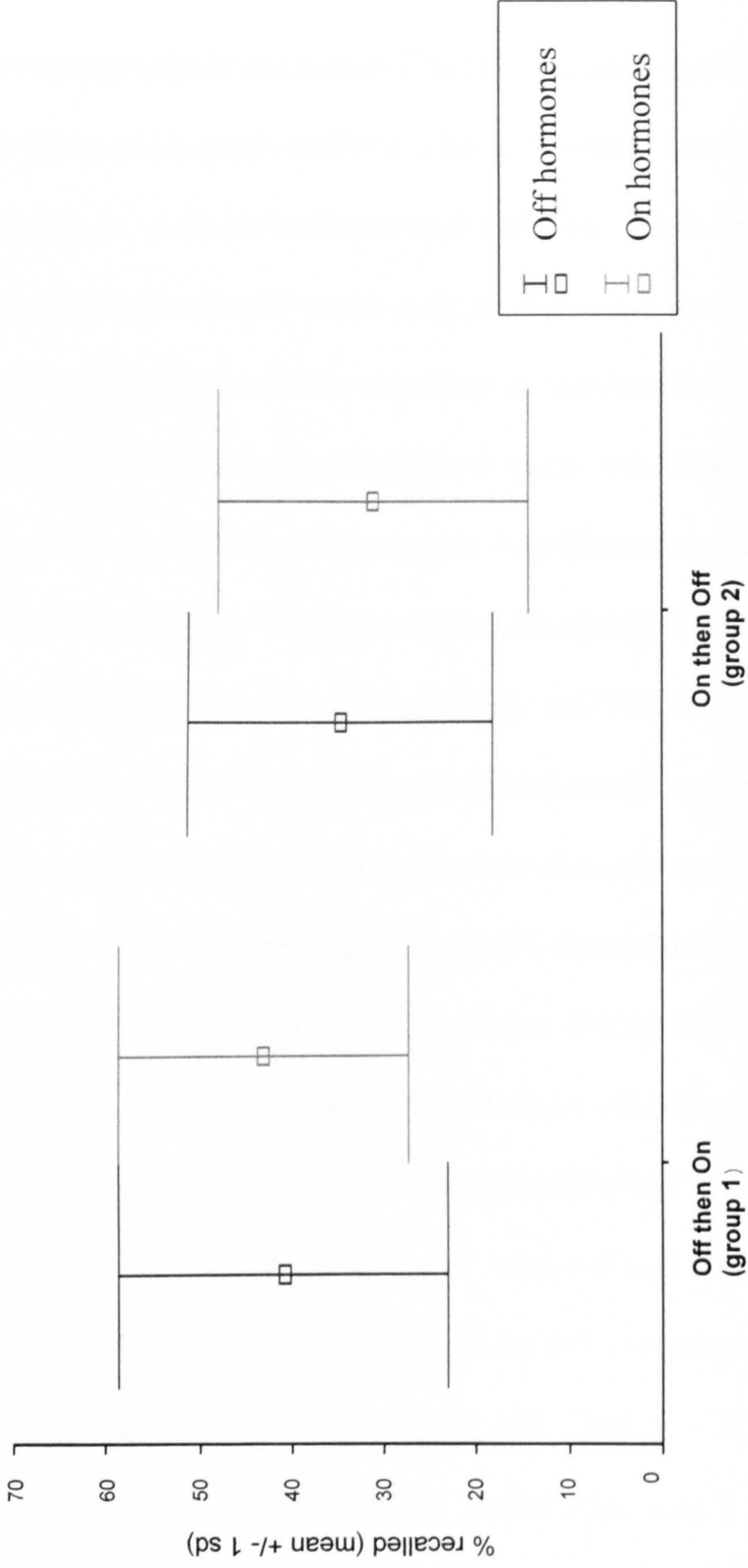
As outlined in the introductory chapter a symptom of anxiety can be lack of concentration. Therefore, this analysis controlled for levels of anxiety and concentration that may confound research into hormonal influences on cognition.

Due to between group differences in Composed / Anxious, DS Backwards and DS Total scores (which aside from being a control task that shows no sex difference, is also used as a measure of concentration), ANCOVAs were carried out on memory and cognitive measures where a significant correlation was found with these measures ($p < .05$). DS Backwards and DS Total scores did not significantly correlate with any of the other memory or cognitive measures. Composed / Anxious correlated positively with Verbal PAL, trial 1 ($r = .27, p = .053$), LM (delayed recall) ($r = .28, p = .043$) and VR (immediate recall) ($r = .96, p = .008$). When Composed / Anxious was used as a covariate, non-significant group differences in performance on these tasks remained. No relationship was found between mood and either of the concentration measures (Visual Span and DS).

Vocabulary scores correlated positively with the majority of memory and cognitive scores, such that the higher the Vocabulary score the higher patients' scores on the following measures: First and Last names ($r = .32, p = .019$); Mental Rotations ($r = .33, p = .016$); DS Forwards ($r = .51, p = .001$); DS Backwards ($r = .41, p = .002$); DS Total ($r = .53, p = .001$); Verbal PAL, trial 1 ($r = .39, p = .004$); Verbal PAL, trial 2 ($r = .29, p = .035$); Verbal PAL, trial 3 ($r = .34, p = .001$); Verbal PAL, trial 4 (delayed recall) ($r = .38, p = .001$); Visual PAL, trial 2 ($r = .23, p = .021$); Visual

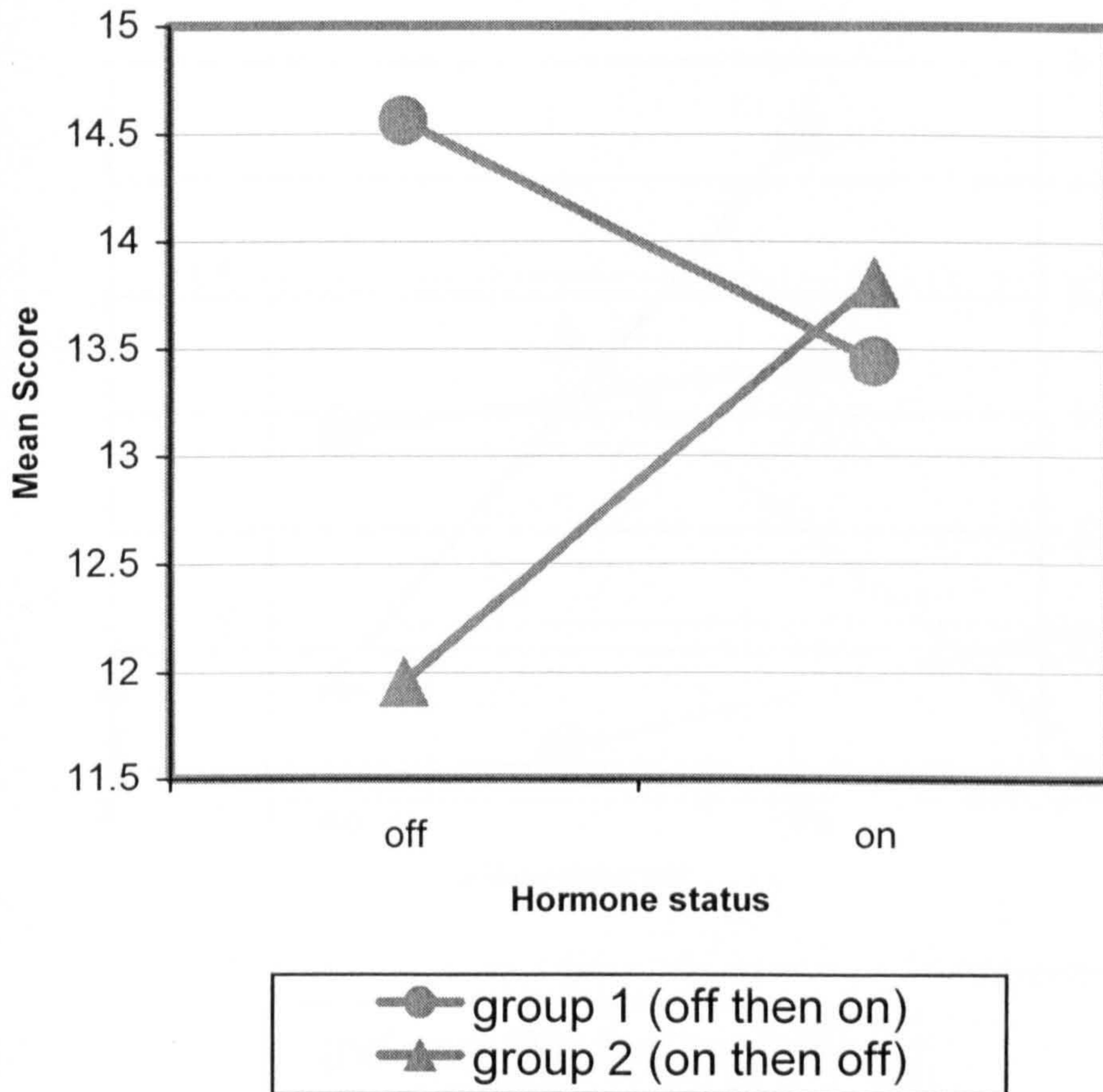
Span Forwards ($r = .40$, $p = .003$); Visual Span Backwards ($r = .43$, $p = .001$); Visual Span Total ($r = .486$, $p = .000$); Visual PAL, trial 3 ($r = .271$, $p = .047$); Visual PAL, trials 1-3 (immediate recall) ($r = .29$, $p = .037$); Controlled Associations ($r = .61$, $p = .001$); Object memory ($r = .36$, $p = .008$); JOLO (Both correct) ($r = .38$, $p = .003$); JOLO (Total correct) ($r = .43$, $p = .001$); FAS ($r = .45$, $p = .001$); VR (immediate recall) ($r = .57$, $p = .001$); VR (delayed recall) ($r = .51$, $p = .001$); LM (immediate recall) ($r = .37$, $p = .006$); LM (delayed recall) ($r = .39$, $p = .037$). For this reason data were reanalysed for these dependent variables using Vocabulary as a covariate. Results of the ANCOVA indicated that within groups differences remained for Digit Span Backwards and Visual PAL, trial 1, but not for Digit Span Total scores. The significant interaction effects between GROUP and HORMONE remained for Object memory and Visual PAL, trial 1 and Visual PAL, trials 1-3 (immediate recall). GROUP differences also remained for LM (delayed recall).

Figure 8: Differences between groups 1 and 2 on LM (delayed recall)



nb: For Group 2 'off' hormone status is 2nd test session. 'on' hormone status is 1st test session

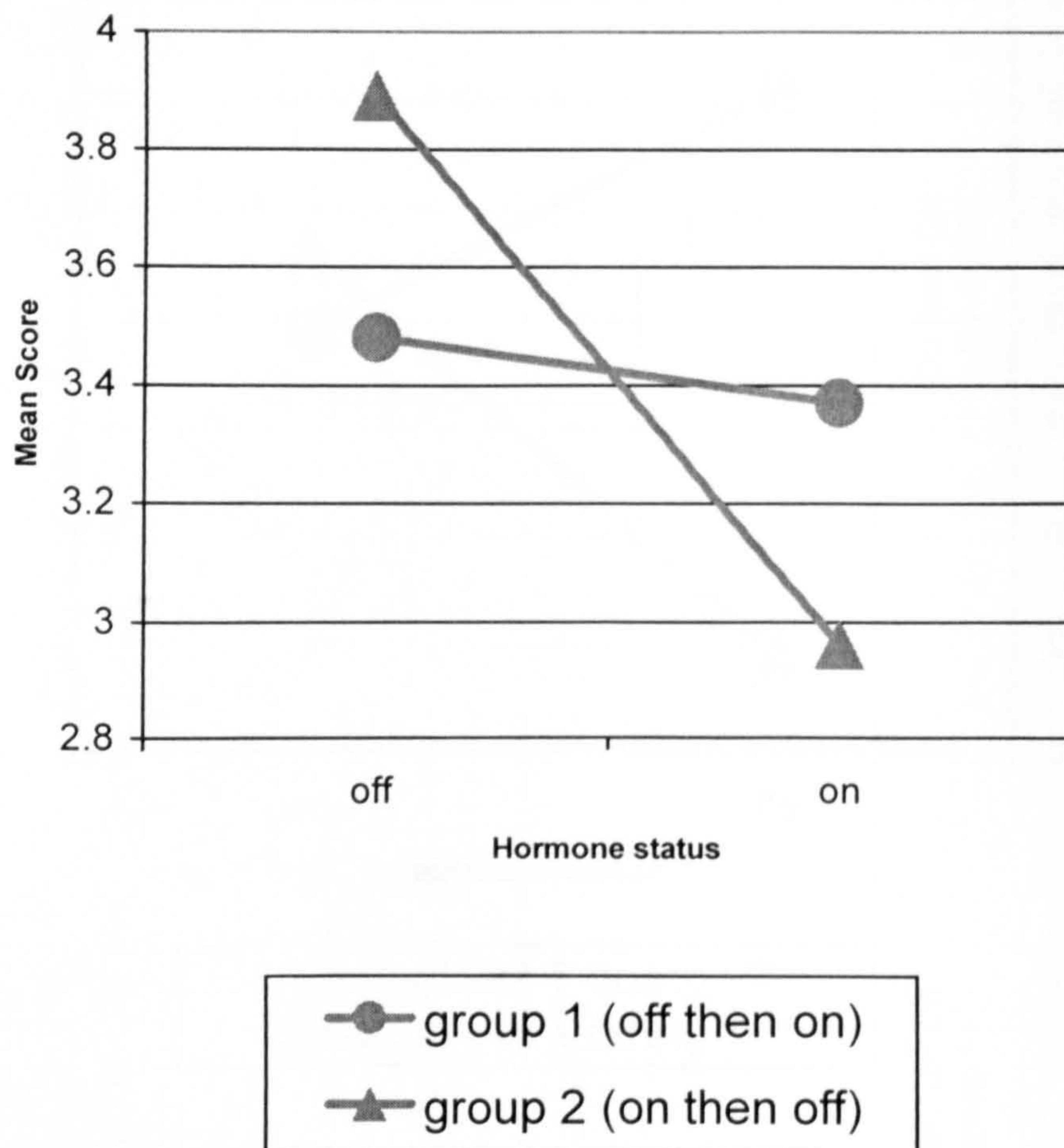
Figure 9: Interaction of Group X Hormone for Object memory



nb: For group two 'off' hormone status was 2nd test session (when withdrawn from hormones). 'on' hormone status was 1st test session.

Figure 10: Interaction of Group X Hormone for Visual PAL -

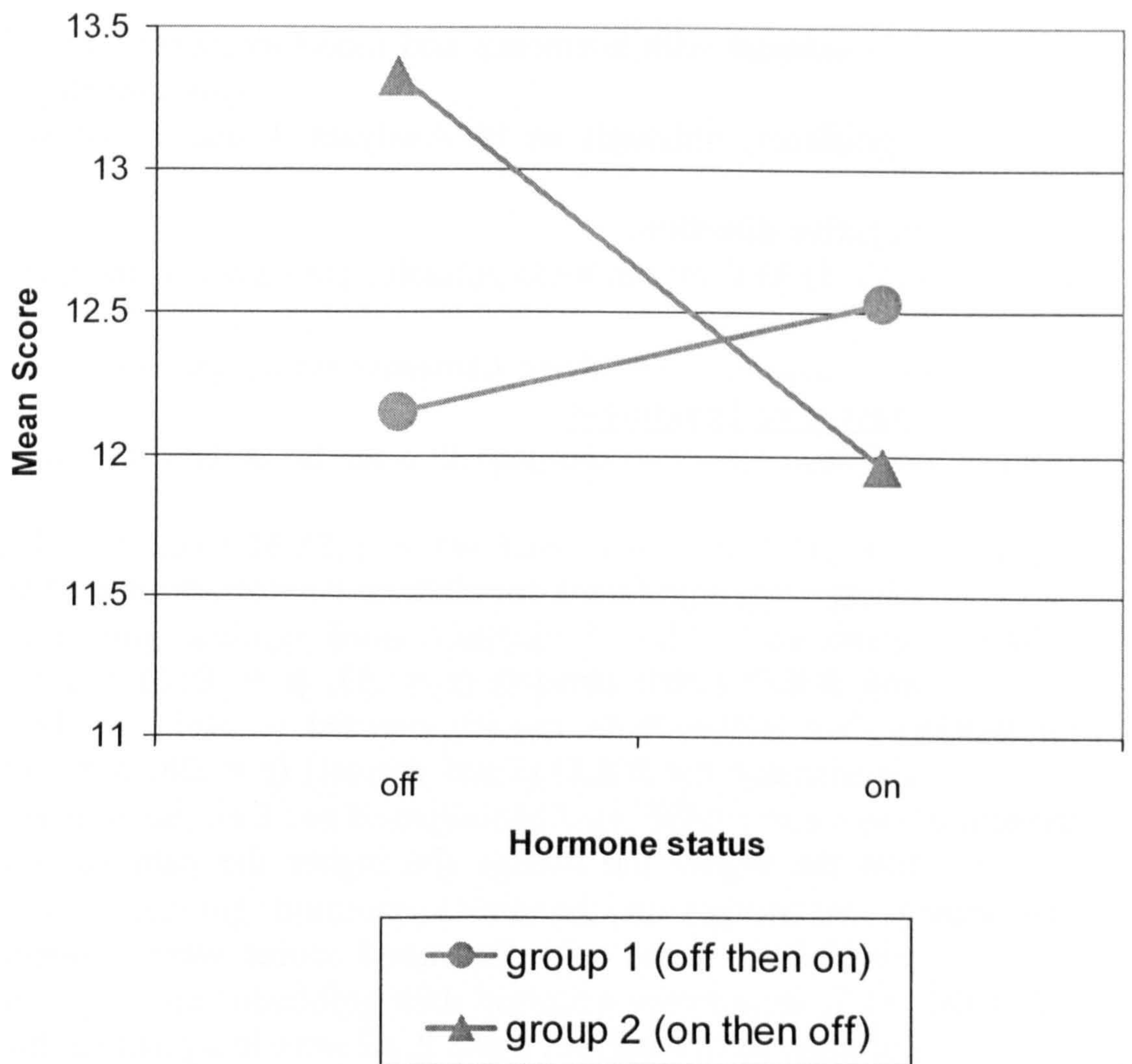
trial 1



nb: For group two 'off' hormone status was 2nd test session (when withdrawn from hormones). 'on' hormone status was 1st test session.

Figure 11: Interaction of Group X Hormone for Visual PAL

(immediate recall)



nb: For group two 'off' hormone status was 2nd test session (when withdrawn from hormones). 'on' hormone status was 1st test session.

Duration of Treatment

Length of treatment correlated negatively with LM (immediate recall) ($r = -.30$, $p = .025$) and LM (delayed recall) ($r = .35$, $p = .009$), such that the shorter the duration of treatment, the higher the score on this task. No other correlations with memory or cognitive scores were significant. Correlations between duration of treatment with hormones and mood measures were also non-significant, although as in Analyses 1 and 2, all were in a negative direction.

Dosage of Treatment

There were significant correlations between dosage of treatment and JOLO (Both correct) ($r = .33$, $p = .016$) and borderline significance for JOLO (Total correct) ($r = .26$, $p = .060$), such that the higher the dosage the higher the patients' score. All correlations found with the mood scores were non-significant, although as in Analyses 1 and 2, all were in a positive direction.

4.3.4. ANALYSIS 4: The three groups analysed separately - Groups 1 (off then on), 2 (on then off) and 3 (control), respectively.

Finally, the three groups were analysed separately using repeated measures MANOVAS. Tables 21, 23 and 25 gives participant characteristics for groups 1 (off then on), 2 (on then off) and 3 (control), respectively.

Group 1 (off then on)

As expected patients were significantly older at time 2 ($F(1, 26) = 28.96, p < .0001$). Vocabulary scores remained stable between time 1 and 2. After hormone administration at time 2, patients became significantly more composed ($F(1, 26) = 16.52, p = .001$) and confident ($F(1, 26) = 6.11, p = .020$), replicating findings from Analyses 1 and 2. The interaction (that approached significance) between factors HORMONE and GROUP for composure in Analysis 3 can be explained here. Whilst this mood improved in those commencing hormone treatment, no significant change was observed in patients coinciding with hormone withdrawal ($F(1, 26) = .14, p = .707$).

Table 25. Participant characteristics for group 1 (off then on hormone treatment).

Variables	Before hormone treatment (mean / SD) TIME 1	During hormone treatment (mean / SD) TIME 2	F	P / ES (d) δ
Age	37.07 / 8.68	37.85 / 8.84	28.96	.001 / 1.5
Composed / Anxious	21.63 / 6.09	25.63 / 7.50	16.52	.001 / 1.15
Agreeable / Hostile	30.07 / 6.45	30.26 / 5.13	.02	.881 / .04
Elated / Depressed	26.00 / 6.41	26.04 / 7.40	.00	.978 / .00.
Confident / Unsure	20.56 / 7.52	24.07 / 7.36	6.11	.020 / .67
Energetic / Tired	19.15 / 10.81	20.93 / 8.53	.11	.431 / .22
Clearheaded / Confused	26.93 / 4.76	27.22 / 5.89	.64	.761 / .08
Sexuality †	7 / 15 / 4 / 1	7 / 15 / 4 / 1		
Vocabulary	5.67 / 7.01	6.70 / 7.55	1.52	.228 / .33
Handedness ‡	5 / 22	5 / 22		
Education ††	5 / 7 / 5 / 1 / 2	5 / 7 / 5 / 1 / 2		

† percentage of sample in respective sexual orientations: heterosexual / homosexual / bisexual / asexual

‡ percentage of sample that are left handed/ right handed

†† percentage of sample in respective education classes: pre O' level / O' level / A' level / Degree / Post – Graduate

δ ES computed repeated measures, using the correlation of the scores between time 1 and time 2 (Cohen. 1988).

nb. For sexuality, education and handedness these variables remain constant.

Memory and cognitive measures

Data for memory and cognitive measures are presented in Table 26.

Table 26: Performance on the memory and cognitive measures for group 1 (off then on hormone treatment)

Measure	Before hormone treatment (mean / SD) TIME 1	During hormone treatment (mean / SD) TIME 2	F	P / ES (d) δ
Mental Rotation	3.22 / 2.62	3.70 / 3.01	.78	.392 / .24
JOLO – Both correct	10.22 / 4.11	10.52 / 4.72	.19	.219 / .13
JOLO – Total correct	27.07 / 7.37	28.11 / 6.85	1.59	.219 / .36
FAS	38.27 / 10.00	40.12 / 12.47	1.30	.265 / .29
Controlled Associations	14.89 / 7.24	13.48 / 6.30	1.73	.200 / -.37
Verbal PAL, trial 1	6.67 / 2.09	6.56 / 2.29	.10	.757 / -.08
Verbal PAL, trial 2	8.11 / 2.14	8.07 / 2.27	.01	.905 / -.03
Verbal PAL, trial 3	8.81 / 1.84	8.70 / 1.77	.12	.736 / -.09
Verbal PAL (delayed recall)	8.81 / 1.64	8.44 / 1.69	3.18	.086 / -.48
First and Last names	4.44 / 3.33	4.33 / 4.05	.07	.799 / -.07
Visual PAL, trial 1	3.48 / 1.99	3.37 / 1.96	.10	.757 / -.09
Visual PAL, trial 2	4.14 / 1.96	4.37 / 1.57	.94	.340 / .29
Visual PAL, trial 3	4.52 / 2.05	4.78 / 1.55	.60	.447 / .21
Visual PAL (immediate recall)	12.15 / 5.54	12.53 / 4.54	.31	.581 / .16
Visual PAL (delayed recall)	4.70 / 1.75	4.52 / 1.76	.40	.531 / -.16
Object memory	14.56 / 4.59	13.44 / 4.51	1.87	.184 / -.38

Table 26 continued

Measure	Before	During	F	P / ES (d) Ω
	hormone	hormone		
	treatment	treatment		
	(mean / SD)	(mean / SD)		
	TIME 1	TIME 2		
Location memory	15.04 / 5.85	15.48 / 6.09	.11	.749 / .08
DS Forwards	7.70 / 2.35	7.85 / 2.49	.17	.681 / .11
DS Backwards	6.00 / 2.39	6.70 / 2.67	5.64	.025 / .66
DS Total	13.70 / 4.06	14.56 / 5.01	3.36	.078 / .54
Visual Span Forwards	8.15 / 2.88	7.85 / 2.35	.47	.500 / -.20
Visual Span Backwards	7.59 / 2.41	7.78 / 2.15	.22	.641 / .13
Visual Span Total	15.74 / 4.78	15.63 / 4.01	.03	.855 / -.10
LM (immediate recall)	45.06 / 19.25	48.99 / 16.65	1.42	.243 / .33
LM (delayed recall)	40.87 / 17.71	43.18 / 15.66	.67	.422 / .23
VR (immediate recall)	17.13 / 4.24	19.15 / 8.82	1.42	.244 / .53
VR (delayed recall)	15.72 / 4.58	18.13 / 7.38	3.20	.085 / .68
Figural memory	7.07 / 1.54	7.11 / 1.91	.01	.917 / .02

Ω ES computed for repeated measures, using the correlation of the scores between time 1 and time 2 (Cohen, 1988).

Separate MANOVAs showed non-significant within group differences between times 1 and 2 on all of the cognitive measures. Patients did not improve on tasks that show sex differences favouring females or deteriorate on tasks that show sex differences favouring males.

Memory measures

DS does not show a sex difference so was used as a control task. However, patients improved with oestrogen treatment on DS Backwards ($F(1, 26) = 5.64, p = .025$). No significant differences were found between time 1 and 2 on DS Forwards. The finding for DS Backwards differs from findings from Analysis 1 where no significant difference on this measure was found between those on and off awaiting hormone treatment.

Analyses of Covariance

Patients during oestrogen treatment were more composed and confident than before treatment. To examine whether these mood changes may have obscured or created significant differences on memory or cognitive measures, several analyses of covariance were conducted. These were used when mood scores correlated with the outcome scores at the conventional level of $p < .05$.

Composed correlated positively with DS Backwards ($r = .55, p = .003$), such that the more composed the patient the higher the score on this task. When this mood was entered into the analysis as a covariate, differences

between time 1 and 2 remained non-significant. As DS measures are used as a measure of concentration, DS Backwards was used as a covariate with the memory, cognitive and mood measures. Differences between times 1 and 2 of testing remained non-significant for all dependent variables.

Vocabulary scores correlated positively with some of the memory and cognitive scores, such that the higher the Vocabulary score the higher patients' scores on the following measures: DS Forwards ($r = .62$, $p = .001$); DS Backwards ($r = .43$, $p = .027$); DS Total ($r = .61$, $p = .001$); Verbal PAL, trial 1 ($r = .65$, $p = .001$); Verbal PAL, trial 2 ($r = .41$, $p = .033$); Controlled Associations ($r = .57$, $p = .002$); JOLO (Both correct) ($r = .49$, $p = .010$); FAS ($r = .45$, $p = .020$); VR (immediate recall) ($r = .60$, $p = .001$); VR (delayed recall) ($r = .55$, $p = .003$). For this reason data were reanalysed for these dependent variables using Vocabulary as a covariate. Results of the ANCOVA indicated that within groups differences remained for Digit Span Backwards. The non-significant differences between those taking hormones and those not taking hormones on the other memory and cognitive measures also remained.

Duration of Treatment

All correlations of the memory and cognitive measures with duration of treatment were non-significant. Duration of treatment was not associated significantly with any of the mood scores and did not show the negative pattern of association (although non-significant) observed in previous analyses.

Dosage of Treatment

Dosage of treatment correlated positively with the LM (immediate recall) ($r = .41, p = .019$) and delayed recall ($r = .48, p = .032$). Positive associations were also found between dosage of treatment and Controlled Associations ($r = .39, p = .046$) and Mental Rotations ($r = .42, p = .029$), such that the higher the dosage, the higher the score on these tasks. Dosage of treatment was also positively associated with how elated ($r = .37, p = .059$) and energetic ($r = .51, p = .007$) the patients felt, such that the higher the dosage the more energetic and elated the patients reported feeling.

Treatment with different hormone combinations

2 patients were taking Androcur in addition to oestrogen. When these patients were excluded, the significant within group differences on composure ($F(1, 24) = 13.01, p = .001$) and confidence ($F(1, 24) = 5.42, p = .029$), remained.

Group 2 (on then off)

Patients were older at time 2 than at time 1 ($F(1, 26) = 19.69, p = <.0001$). Vocabulary scores did not change significantly from time 1 to time 2. The composure or confidence of patients did not differ as a result of hormone withdrawal and so did not parallel the significant changes found in Analyses 1, 2 and 3. The other mood measures also did not differ between time 1 and 2. This would explain the reduced significance obtained for group differences in Composed / Anxious when group 1 and 2 were combined in Analysis 3.

Table 27. Participant characteristics for group 2 (on then off hormone treatment).

Variables	During hormone treatment (mean / SD) TIME 1	Withdrawal from hormone treatment (mean / SD) TIME 2	F	P / ES (d) Ω
Age	39.63 / 9.68	40.22 / 9.83	19.69	.000 / - 1.5
Composed / Anxious	23.11 / 6.55	22.52 / 7.38	.14	.707 / .10
Agreeable / Hostile	29.48 / 5.64	30.70 / 6.68	.88	.358 / -.26
Elated / Depressed	23.96 / 7.33	24.33 / 8.14	.05	.819 / -.07
Confident / Unsure	20.81 / 6.59	21.00 / 8.05	.01	.922 / -.03
Energetic / Tired	23.96 / 7.33	18.85 / 8.99	.00	.985 / .05
Clearheaded / Confused	25.26 / 6.81	24.19 / 6.71	.57	.456 / .21
Sexuality †	3 / 14 / 7 / 3	3 / 14 / 7 / 3		
Vocabulary	5.19 / 6.47	5.37 / 7.41	.03	.871 / -.04
Handedness ‡	3 / 24	3 / 24		
Education ‡‡	9 / 10 / 4 / 2 / 2	9 / 10 / 4 / 2 / 2		

† percentage of sample in respective sexual orientations: heterosexual / homosexual / bisexual / asexual

‡ percentage of sample that are left handed/ right handed

‡‡ percentage of sample in respective education classes: pre O' level / O' level / A' level / Degree / Post – Graduate

Ω ES computed repeated measures, using the correlation of the scores between time 1 and time 2 (Cohen. 1988).

nb. For sexuality, education and handedness these variables remain constant.

Table 28: Performance on the memory and cognitive measures for group 2 (on then off hormone treatment).

Measure	During hormone treatment (mean / SD) TIME 1	Withdrawal from hormone treatment (mean / SD) TIME 2	F	P / ES (d) δ
Mental Rotation	3.07 / 1.90	3.07 / 2.20	.00	1.000 / .00
JOLO – Both correct	11.23 / 5.95	10.04 / 4.11	1.71	.203 / .38
JOLO – Total correct	28.54 / 5.96	28.07 / 5.66	.23	.634 / .13
FAS	37.26 / 11.60	38.85 / 15.94	.60	.445 / -.24
Controlled Associations	13.80 / 7.50	15.30 / 8.89	.86	.365 / -.35
Verbal PAL, trial 1	6.67 / 2.09	6.56 / 2.29	.22	.640 / .55
Verbal PAL, trial 2	8.11 / 2.14	8.07 / 2.27	.20	.659 / .03
Verbal PAL, trial 3	8.62 / 1.52	8.52 / 1.40	.14	.709 / .09
Verbal PAL (delayed recall)	8.19 / 2.17	8.04 / 1.93	.14	.708 / .10
First and Last names	3.81 / 3.37	4.54 / 4.22	2.65	.116 / -.45
Visual PAL, trial 1	2.96 / 1.72	3.89 / 1.93	5.91	.022 / -.67
Visual PAL, trial 2	4.19 / 1.71	4.44 / 1.67	.52	.478 / -.19
Visual PAL, trial 3	4.81 / 1.67	4.96 / 1.61	.24	.631 / -.13
Visual PAL (immediate recall)	11.96 / 4.20	13.33 / 4.67	2.86	.103 / -.46
Visual PAL (delayed recall)	4.52 / 1.63	4.93 / 1.62	1.45	.240 / -.32
Object memory	13.81 / 4.94	11.96 / 5.12	3.07	.091 / .48
Location memory	15.04 / 5.85	15.48 / 6.09	.11	.749 / -.08
DS Forwards	7.74 / 1.99	7.52 / 1.97	.63	.433 / .21
DS Backwards	6.63 / 1.94	5.96 / 2.03	3.18	.086 / .49
DS Total	14.37 / 3.39	13.48 / 3.42	2.79	.107 / .46
Visual Span Forwards	8.19 / 1.54	7.89 / 1.50	.82	.375 / .25

Table 28 continued

Measure	During hormone treatment (mean / SD) TIME 1	Withdrawal from hormone treatment (mean / SD) TIME 2	F	P / ES (d) δ
Visual Span Backwards	8.04 / 2.03	7.26 / 1.75	3.84	.061 / .53
Visual Span Total	16.22 / 3.03	15.15 / 2.16	3.59	.069 / .53
LM (immediate recall)	40.41 / 16.36	42.82 / 15.32	.80	.381 / -.24
LM (delayed recall)	32.16 / 16.15	34.75 / 16.52	1.49	.234 / -.30
VR (immediate recall)	17.20 / 3.53	17.26 / 4.01	.01	.939 / -.02
VR (delayed recall)	15.22 / 4.19	15.37 / 4.95	.03	.873 / -.04
Figural memory	6.89 / 1.31	7.30 / 1.75	2.06	.163 / .41

δ ES computed repeated measures, using the correlation of the scores between time 1 and time 2 (Cohen. 1988).

Data for memory and cognitive measures are presented in Table 28.

Cognitive measures

There were no significant differences from patients' performance at time 1 (on hormone treatment) to time 2 (withdrawal from hormone treatment) on any of the cognitive tests. Patients did not improve on tasks that show sex differences favouring males or deteriorate on tasks that show sex differences favouring females.

Memory measures

Relating back to the interaction effects found in Analysis 3 on Object memory, Visual PAL, trial 1 and the composite score for Visual PAL, trials 1-3 (immediate recall), there was a significant difference between performance at time 1 and 2 on Visual PAL, trial 1 ($F(1, 26) = 5.91, p = .022$), such that when patients were withdrawn from hormones they did better than when they were taking hormones. A similar pattern also was found for the composite score of Visual PAL, trials 1-3 (immediate recall), however significance was lower than the conventional level with ($F(1, 26) = 2.86, p = .10$). For both of these measures there was no significant difference in group 1 (off then on) when on versus off hormones ($F(1, 26) = .10, p = .757$) and ($F(1, 26) = .31, p = .581$, respectively)). This could explain the significant interaction effect on these measures in Analysis 3.

For Object memory, however, group 2 (on then off) performed better when taking hormones at time 1 although significance was lower than the conventional level ($F(1, 26) = 3.07, p = .09$). No significant changes were observed between test session 1 and 2 in group 1 ($F(1, 26) = 1.87, p = .184$). Again, this could explain the significant interaction effect seen for these variables in Analysis 3.

Analyses of Covariance

None of the 6 moods or age correlated significantly with any of the memory or cognitive measures. Vocabulary scores correlated positively with some of the measures, such that the higher the Vocabulary score the higher patients' scores on the following measures: First and Last names ($r = .44$, $p = .023$); DS Forwards ($r = .56$, $p = .002$); Controlled Associations ($r = .62$, $p = .001$); JOLO (Total correct) ($r = .45$, $p = .019$); FAS ($r = .49$, $p = .010$); VR (delayed recall) ($r = .49$, $p = .010$). For this reason data were reanalysed for these dependent variables using Vocabulary as a covariate. Results of the ANCOVA indicated that within groups differences remained for Object memory and Visual PAL, trial 1 and Visual PAL, trials 1-3 (immediate recall).

Duration of Treatment

Duration of treatment correlated positively with Visual PAL, trial 2 ($r = .48$, $p = .01$) and the composite score for Visual PAL, trials 1-3 (immediate recall) ($r = .23$, $p = .02$), such that those who had been on hormones for a longer time did better than those who had been on for a shorter time. Duration of treatment was not associated with any other memory, cognitive or mood scores.

Dosage of Treatment

Dosage of treatment did not correlate significantly with any of the memory, cognitive or mood measures at the conventional level ($p < .05$).

Treatment with different hormone combinations

When those treated with oestrogen only were compared with those taking oestrogen with either Provera or Androcur, within group differences remained non-significant. Within group differences in the variables that were significant remained.

Group 3 (controls – on then on)

To determine any practise or boredom effects the performance of the control group at time 1 and 2 was compared using repeated measures MANOVAs.

Table 29. Participant characteristics for group 3 (control group: on hormones at Time 1 and 2).

Variables	On hormone treatment (mean / SD) TIME 1	On hormone treatment (mean / SD) TIME 2	F	P / ES (d) Ω
Age	40.30 / 7.50	40.60 / 7.71	9.24	.007 / 1.33
Composed / Anxious	28.75 / 5.49	28.50 / 7.66	.03	.860 / -.06
Agreeable / Hostile	31.05 / 3.93	29.80 / 6.51	.77	.392 / -.29
Elated / Depressed	29.00 / 4.60	27.05 / 5.89	1.56	.227 / -.40
Confident / Unsure	25.1 / 7.23	25.60 / 8.71	.06	.812 / .07
Energetic / Tired	21.40 / 7.21	23.60 / 7.97	1.06	.315 / .32
Clearheaded / Confused	30.15 / 5.42	27.90 / 4.91	2.93	.103 / -.71
Sexuality †	8 / 5 / 5 / 2	8 / 5 / 5 / 2		
Vocabulary	5.80 / 6.35	5.55 / 5.03	.07	.796 / -.08
Handedness ‡	16 / 4	16 / 4		
Education ††	5 / 7 / 5 / 1 / 2	5 / 7 / 5 / 1 / 2		

† percentage of sample in respective sexual orientations: heterosexual / homosexual / bisexual / asexual

‡ percentage of sample that are left handed/ right handed

†† percentage of sample in respective education classes: pre O' level / O' level / A' level / Degree / Post – Graduate

Ω ES computed repeated measures, using the correlation of the scores between time 1 and time 2 (Cohen. 1988).

nb. For sexuality, education and handedness these variables remain constant.

Besides the age increase of patients at time 2 ($F(1, 26) = 9.24, p = .007$), characteristics resemble those found for group 2, in that patients did not differ between time 1 and 2 on Vocabulary or any of the mood measures.

Table 30: Performance on the memory and cognitive measures for group 3 (control group: on hormones at Time 1 and 2).

Measure	On hormones at time 1 (mean / SD)	On hormones at time 2 (mean / SD)	F	P / ES (d) η^2
Mental Rotation	3.65 / 2.62	3.85 / 2.80	.11	.750 / .10
JOLO – Both correct	10.65 / 3.31	11.35 / 2.94	1.43	.246 / .37
JOLO – Total correct	28.60 / 4.74	29.70 / 3.73	1.87	.187 / .45
FAS	38.75 / 10.68	41.30 / 13.85	1.85	.190 / .31
Controlled Associations	13.80 / 7.50	15.30 / 8.89	.86	.365 / .30
Verbal PAL, trial 1	6.10 / 1.65	6.85 / 1.63	3.25	.087 / .59
Verbal PAL, trial 2	8.15 / 1.63	8.35 / 1.60	.27	.612 / .16
Verbal PAL, trial 3	8.90 / 1.45	8.85 / 1.18	.04	.841 / -.07
Verbal PAL (delayed recall)	8.35 / 1.63	8.45 / 1.76	.11	.741 / .09
First and Last names	4.30 / 4.14	4.95 / 3.56	1.11	.305 / .34
Visual PAL, trial 1	3.30 / 1.81	3.85 / 1.76	1.35	.259 / .37
Visual PAL, trial 2	4.55 / 1.32	4.90 / 1.59	1.35	.260 / .37
Visual PAL, trial 3	4.85 / 1.35	5.15 / 1.14	1.69	.209 / .41
Visual PAL (immediate recall)	12.70 / 3.51	13.90 / 3.97	2.86	.107 / .54
Visual PAL (delayed recall)	5.00 / 1.30	5.05 / 1.50	.04	.841 / .07
Object memory	13.10 / 4.28	12.65 / 5.38	.27	.608 / -.16
Location memory	114.30 / 5.70	15.80 / 6.07	.73	.403 / .27

Table 30 continued

Measure	On hormones at time 1 (mean / SD)	On hormones at time 2 (mean / SD)	F	P / ES (d) Ω
DS Forwards	8.05 / 2.11	8.45 / 2.11	1.75	.202 / .42
DS Backwards	7.00 / 2.49	7.25 / 2.75	.40	.536 / .21
DS Total	14.95 / 3.94	15.70 / 4.45	2.23	.152 / .49
Visual Span Forwards	8.55 / 1.28	7.90 / 2.25	1.66	.213 / -.70
Visual Span Backwards	7.65 / 1.31	8.05 / 2.31	.81	.379 / .31
Visual Span Total	16.20 / 1.96	15.95 / 3.79	.14	.714 / .15
LM (immediate recall)	38.68 / 11.17	46.41 / 10.25	8.42	.009 / .78
LM (delayed recall)	33.35 / 13.75	40.70 / 11.90	6.45	.020 / .71
VR (immediate recall)	17.32 / 3.70	17.63 / 3.20	.11	.736 / .11
VR (delayed recall)	15.11 / 4.02	16.38 / 3.52	3.02	.099 / .57
Figural memory	6.60 / 1.57	7.80 / 1.36	9.24	.007 / 1.14

Ω ES computed repeated measures, using the correlation of the scores between time 1 and time 2 (Cohen, 1988).

Memory, Cognitive and mood measures

Data for memory and cognitive measures are presented in Table 26.

There were no significant differences between patients' performance at time 1 (on hormone treatment) and time 2 (still on hormone treatment) on the majority of tests. Patients did improve on several of the tasks at time 2, indicating possible practice effects. Patients did not differ between times 1 and 2 on any of the mood measures.

Memory measures

There was a significant difference between performance at time 1 and 2 on LM (immediate recall) ($F(1, 19) = 8.42, p = .009$), LM (delayed recall) ($F(1, 19) = 6.45, p = .020$) and Figural memory ($F(1, 19) = 9.24, p = .009$) such that patients improved on these tasks at time 2. Concentration as measured by DS and Visual Memory Span did not significantly change in the patients between first and second test sessions for those on hormone treatment at both times.

Cognitive measures

Performance did not significantly change from time 1 to 2 on any of the other cognitive measures.

Analyses of Covariance

Vocabulary scores correlated positively with the majority of memory and cognitive scores, such that the higher the Vocabulary score the higher patients' scores on the following measures: Verbal PAL, trial 1 ($r = .47, p = .037$); Verbal PAL, trial 3 ($r = .47, p = .035$); Controlled Associations ($r = .59, p = .006$); FAS ($r = .46, p = .042$). For this reason data were reanalysed

for these dependent variables using Vocabulary as a covariate. Results of the ANCOVA indicated that within groups differences remained for LM (delayed recall) and Figural memory.

Duration of Treatment

Duration of treatment correlated positively with Visual Memory Span backwards ($r = .57, p = .008$) and Visual Memory Span total scores ($r .61, p = .004$), but not with any other memory or cognitive measure.

Dosage of Treatment

There were no significant correlations between dosage of treatment and any cognitive, memory or mood measures.

Treatment with different hormone combination

When those treated with oestrogen only were compared with those taking oestrogen with either Provera or Androcur, within group differences remained non-significant. Within group differences in the variables that were significant remained.

4.4. DISCUSSION

The purpose of this discussion is to address the aims outlined in the introduction in light of the empirical results obtained in the study. Each will be addressed separately.

4.4.1. Replication of previous findings from Chapter 2

In Chapter 2 a significant difference was found in performance on Verbal PAL between M-F transsexuals taking cross-sex hormones and those not taking cross-sex hormones. This preliminary study showed that those patients taking hormones scored higher on this task than those not taking hormones. No difference was found on any of the other memory or cognitive tasks. The present findings with a different group of M-F transsexuals only partially replicate these former data. Whilst there was no difference between those taking hormones and those not taking hormones on the same tests used in the preliminary study, there was also no difference between groups on the Verbal PAL task. These results occurred when groups were matched on factors such as age and education and when those taking oestrogens exclusive of Androcur or Provera compared with non-users were analysed.

The group taking hormones were older than those not taking hormones. Age correlated negatively with Visual PAL scores such that the younger the patients, the higher they scored on this task. This negative association between age and Visual PAL replicates previous associations between age and PAL and other secondary memory tasks. As in the present study, others have also found no associations between age and primary memory tasks (Gilbert and Levee, 1971). However, in the current study, when age was controlled, group differences remained non-significant. Furthermore as there were no group differences in Vocabulary, sexual orientation, education and handedness, it is unlikely that these factors masked any hormonal influence on memory and cognition.

4.4.2. Within Subjects results in memory and cognition

The present study was superior to the between subjects design in Chapter 2. With participant characteristics of age, Vocabulary, education, sexual orientation and handedness eliminated, monitoring the same patient throughout treatment would be more powerful and sensitive to changes not detected in the previous between group analyses.

Overall the findings were negative and given the number of statistical comparisons made for each group using MANOVA (31), any significant differences could have been due to chance. However, the few significant differences observed will be discussed in light of other research.

One aim of this study was to determine whether a change in performance would be observed in those just commencing treatment e.g., towards an enhancement on tasks at which females excel and a decline in performance on tasks at which males excel. Another aim was to examine whether withdrawal of hormones prior to surgery, as prerequisite to SRS, produced changes in cognitive and memory performance e.g., towards a decline in performance on tasks at which females excel or an improvement on tasks at which males excel. Several changes in memory were observed.

In those commencing treatment, performance on a test of concentration, DS Backwards, was enhanced, whereas withdrawal of hormone treatment did not coincide with a decline in performance on this task. Although this task is verbal in nature, it does not show a sex difference (Blum et al, 1972; Chavez et al, 1983). This result does not match what would be predicted for a hormonal effect. The difference seen in performance in those commencing treatment is probably caused by factors other than oestrogen

treatment. For instance, patients might be relieved and pleased to be moving forward towards their goal of sex re-assignment and might therefore have increased powers of concentration, leading to improved performance on DS.

A different pattern was seen for performance on the Visual PAL memory task. Here the pre-surgical group showed a significant improvement following withdrawal from hormone treatment, whereas no change in performance was found as a result of commencing treatment. Although research has not yet established a sex difference on this task, one could hypothesise, based on the visual nature of this task, that it might favour males. The pre-surgical patients also showed a decline in Object memory, a task favouring females (Silverman and Eals, 1992), after hormone withdrawal. However, patients did not improve in performance on this task after commencing treatment. Therefore, for the memory and cognitive tasks, findings do not give a clear-cut idea of whether the impact of hormones on memory and cognition is more dramatic as a result of commencing or withdrawal of hormone treatment. In addition, hormone effects suggested by cognitive change following initiation of treatment were not verified by reciprocal changes following cessation of treatment. Similarly, changes seen following treatment cessation were not verified by

reciprocal changes following treatment initiation. Therefore, the few changes seen might prove to be unreliable. These inconsistent findings suggest that the performance changes observed may not be hormone effects. The few changes seen could have resulted given the large number of comparisons and the small number of significant differences.

As the control group was used to ascertain whether practice or boredom effects occurred on any of these measures, it is of note that there were significant differences on two of the dependent measures. Patients improved on LM and Figural memory at the second test session even though their hormone treatment was not manipulated in any way. This suggests that there could be changes in performance between first and second test session due to order effects rather than hormonal manipulation. However, for the tasks there were no changes in performance in the two groups where hormonal status was altered between first and second test session. One could argue that this lack of change in these groups is important, such that oestrogen treatment might impair performance on these tasks.

4.4.3. Hormonal influences on mood

Between group differences, whether using the full sample, the oestrogen-only group, or groups matched on age and education were consistently found in composure and confidence. Patients taking hormones were more composed and confident than those not taking hormones (irrespective of whether they were commencing treatment or in the presurgical group). When those taking oestrogen in addition to other hormones such as Provera or Androcur were excluded the magnitude of this difference was greater. These results are similar to results found in Chapter 2 where there was some evidence of a more positive mood in the group taking oestrogen compared to the group awaiting hormone treatment, although this was non-significant. Findings were also consistent with past research, which suggests that the addition of progesterone in combined forms of HRT may oppose some mood enhancements of oestrogen (Sherwin, 1991). Those taking oestrogen only were also more clearheaded than those not taking oestrogen. Non-significant and significant differences in cognitive tasks remained when these moods were statistically controlled.

The enhanced mood observed in the between subjects analysis, was investigated in more detail when there was a comparison between those commencing treatment and those withdrawing from hormone treatment. When these two groups were separated, those awaiting treatment were less composed and confident than when they were later undergoing hormone treatment. Withdrawal of treatment prior to surgery however did not coincide with any change in these moods. This suggests that if hormones cause the change in mood, this influence on mood is restricted to initiation of treatment and is not reversed by withdrawal of hormones, at least for the time period (8 weeks) investigated in this study. However, It is possible that the washout period of eight weeks was not sufficiently long to cause the necessary reduction in female hormone in which a change of mood can be noticed. Alternatively, the mood improvement may be the result of the patients' happiness at moving forward with their treatment program. No within group findings were detected on any of the other moods. Furthermore, no change in mood was found in the control group.

4.4.4. Relating results to past research into oestrogenic effects on memory and cognition.

The present findings are not consistent with past reports of improved verbal memory after ERT administration to spontaneously postmenopausal or surgically postmenopausal women (See Sherwin, 1996, 1997 and 1999 for reviews). Verbal PAL has also been reported to not differ in women during the menstrual and luteal phases of the menstrual cycle (Richardson, 1991). The changes observed in the current study may support other findings that HRT may facilitate other aspects of cognition irrespective of sex differences, in that women on HRT perform better than those not on HRT on a variety of cognitive measures (Kimura, 1995; Hogervorst et al, 1999; Duka et al, 2000). Indeed, Carlson and Sherwin (1998) report that elderly oestrogen users had higher scores on DS than non-oestrogen users. As DS is a task showing no sex difference (Blum et al, 1972; Chavez et al, 1983) these findings could suggest that oestrogenic influences on memory and cognition may not be restricted to tasks that are sexually dimorphic.

Furthermore it is also possible that in these previous studies of women, non-hormonal factors could explain the group differences. For instance,

women who seek out and choose to take HRT may be more educated or intelligent than those who do not.

Some prior research into cognitive abilities during the menstrual cycle suggested an enhancement of verbal abilities on tasks that favour females when oestrogen levels are high along with a decline in performance on tasks that favour males (Hampson and Kimura, 1998; Hampson 1990 a, b, and c; Hausmann, Slabbekoorn, Van Goozen, Cohen-Kettenis, Guentuerkuen, 2000; Weekes, 1997). Thus the finding in the current study that performance on Object memory declined in patients when they were withdrawn from hormone treatment (group 2 - on then off) could be consistent with the hypothesis that oestrogen enhances performance on tasks at which females excel. Meta-analytic findings from Chapter 3 suggest that there is a sex difference in Object memory. Among the 13 studies reviewed for this task, the sex difference was statistically significant from zero, however using the fail safe method (Rosenthal, 1979) only approximately 22 additional studies showing negative findings would be needed to reverse the conclusion of a significant sex difference. Therefore, the studies that show sex differences on this task may be biased and not representative of all the studies examining sex differences on this task. In addition, Gaulin et al, (1997) did not find a positive correlation of

oestrogen levels during the menstrual cycle with Object memory and a complimentary change was not seen in the group of participants tested before and after hormone treatment (group 1 – off then on).

Performance on the visual memory task (Visual PAL, immediate recall) improved when patients were withdrawn from hormone treatment. Although there is no established sex difference on this task, this task is of a visual nature and further research might reveal a sex difference favouring males. Therefore, one could suggest that this finding partially supports previous reports that M-F transsexuals receiving cross-sex hormones show impairment on visual-spatial tasks that favour males and enhancement on verbal tasks favouring females (Van Goozen et al, 1995). This interpretation however is fragile, as a later attempt failed to replicate activational influences of oestrogen on Verbal Fluency in a different group of M-F transsexuals. Furthermore, the authors did not specifically use Visual PAL in these studies (Slabbekoom et al, 1999; Van Goozen et al, 1995). Similarly, in the current study this pattern of visual-spatial performance deterioration coinciding with verbal performance enhancement was not demonstrated on the majority of other measures that show reliable sex differences. In addition, Verbal PAL did not decline in the current study when patients were withdrawn from hormone treatment.

As this is a verbal analogue to Visual PAL, the results do not conform to the predicted pattern of a hormone effect on memory and cognition e.g., a reciprocal change of an increase in Verbal PAL alongside a decline in Visual PAL was not seen in those commencing treatment.

It is of importance when interpreting the present findings to acknowledge that the majority of studies cited looking at the effects of oestrogen on cognitive abilities have focused on women. As men and women differ on more than hormones, e.g., in terms of chromosomes, prenatal organising effects, genitalia, socialisation experiences and other behaviours, etc., it is possible that the observed oestrogenic effects on cognition in women do not apply to men. As with the findings from Chapter 2 additional research is needed to determine why prior findings on women suggesting that oestrogen impairs performance on tasks favouring males (e.g., Mental Rotations and JOLO) and improves performance on tasks favouring females (e.g., Controlled Associations and Verbal Fluency) were not supported in our sample. Furthermore, it is possible that the few changes observed in the present sample might have related to factors other than hormones or has been chance findings.

4.4.5. Relating results to past research into oestrogenic effects on mood.

Our mood findings are consistent with those outlined in the introductory chapter. Low oestrogen is associated with negative feelings in menopausal women (see Halbreich, 1997 for review), women undergoing postnatal depression (Harris, 1996) and women during their menstrual cycle (Gaulin et al, 1997). Furthermore, the present findings parallel those found in non gender dysphoric men. Positive changes in mood have been observed in men with dementia as a consequence of low dose oestradiol therapy (Kay et al, 1995). Also, in clinically depressed women, those taking antidepressants alongside ERT improve more than those taking antidepressants only (Schneider et al, 1997; Amsterdam et al, 1999). Finally, the present study confirms past research of a positive effect of cross-sex hormones on mood after short-term therapy. Van Goozen, Cohen-Kettenis, Gooren, Frijda and Van de Poll (1995) found M-F transsexuals to be less prone to anger and aggression after oestrogen treatment than before their treatment. Withdrawal of long-term hormone treatment did not result in a change in mood. Such long-term mood effects cannot be ruled out, as it is unclear whether the period of cessation was sufficiently long. This lack of reciprocal change may be due to factors other than hormones.

4.4.6. Duration and dosage of treatment

Little evidence was found that duration of treatment correlated with performance on memory or cognitive measures. Further, the few significant correlations could be due to chance. In addressing associations of duration and dosage of hormone treatment on performance and mood, 70 correlations for each analysis were conducted and few were found significant. However, the findings will be discussed in light of other research.

4.4.7. Duration of treatment – Between and within groups – Memory and Cognition

When all patients taking hormones were included in the analysis no significant correlations were found. When those taking oestrogen only were analysed a significant positive association of duration of treatment with Visual Span Backwards (a task that meta-analytic results in Chapter 3 suggest may favour males) and JOLO scores was observed, suggesting that the longer a patient is on treatment the higher their scores on this task. For a task favouring females (Object memory) significant negative correlations were found only in the matched group analysis (Analysis 2), suggesting that the shorter the duration of treatment the higher their scores on these

tasks. All of these correlations are in the opposite direction of prediction based on the idea that oestrogen enhances abilities at which females excel and impairs those at which males excel, assuming that longer treatment would provide a more powerful oestrogenic effect. No other associations were found. In addition, the few significant correlations for duration of treatment with memory and cognitive scores were not replicated across analyses therefore results are unreliable.

Within groups – Memory and Cognition

For the collapsed group analysis, a negative association for duration of treatment with LM, immediate and delayed recall scores only was found. Conversely, in the pre-surgical group, positive associations were found for duration of treatment with Visual PAL, trials 2 and 3 (a task hypothesised to favour males due to its visual nature). In this group, the longer the person had taken hormones the higher their scores on this task. In those commencing treatment no significant associations in any consistent direction were found. Similar to the between groups (oestrogen only) analysis, for those on oestrogen only, a positive correlation was found for duration of treatment with Visual Span scores. Results may suggest that for some tasks that favour males performance correlates positively with

duration of treatment, whereas for all those tasks that favour females performance correlates negatively with duration of treatment. This is opposite to the hypothesis that in M-F transsexuals oestrogen treatment would be associated with an enhancement in memory and cognitive abilities at which females excel and be associated detrimentally in memory and cognitive abilities at which males excel.

4.4.8. Duration of treatment – Between and within groups – Mood

For mood, duration of treatment was not significantly associated with any of the moods, although across all between group analyses the association between duration of treatment and all moods was in a negative direction.

Within groups

For the collapsed groups analysis, the negative associations found between duration of treatment and mood paralleled the between group findings. However when groups were separated by stage of treatment, correlations were not significant and in no consistent direction.

4.4.9. Dosage of treatment – Between and Within groups – Memory and Cognition.

Where significant correlations were found between dosage of treatment and performance on memory and cognitive tasks, all were in the positive direction. When all patients were included, positive associations were found with JOLO scores. Positive associations were found for dosage with DS, JOLO and LM (delayed recall) in the group taking oestrogen only. This suggests that the higher the dosage of hormone treatment the higher

the patients scored on these tasks. These associations were not replicated in the matched groups, however.

Within groups

Positive correlations of dosage with JOLO scores were also found in the collapsed groups. However, when groups were separated, results were non-significant and in a non-specific direction.

4.4.10. Dosage of treatment – Between and within groups - Mood

For the between group analyses, there were no significant associations found for dosage of treatment with any of the moods. However, as with the memory and cognitive measures, all associations were in a positive direction, suggesting that the higher the dosage of treatment the more positive the patients felt.

Findings were more complex for within group analyses. For the collapsed groups analysis, the non-significant positive findings found between dosage and mood paralleled between group findings. When groups were separated this pattern was not consistent. For those commencing treatment, dosage was significantly positively associated with how elated and energetic

patients felt. For the presurgical and control groups, correlations of dosage with mood were not significant and did not follow any specific direction.

These associations do not support duration and dosage effects on memory in rat studies. Such research has suggested that short-term treatment with either high or low dosages of oestrogen improves memory, whereas long-term treatment does not (Williams, 1996). While rat studies suggest that dosage may not be important, the present findings of the importance of dosage cannot be ruled out as duration and dosage correlations with memory, cognition and mood scores are inconsistent in direction and unreliable. Where significant associations were found, these were not replicated across analyses for the specific tests.

4.5. Interpretations of the present study

There are limitations to the present study that may explain why the majority of measures used did not demonstrate oestrogenic influence in this particular population.

Firstly, mood enhancements in composure and confidence were demonstrated in the group commencing treatment, but not in the presurgical group. It is possible that the self-report responses of mood from the patients may not have been a hormonal effect. It has been suggested that the beneficial effect of HRT on mood may be due to expectancy effects of patients (Hogervorst et al, 1999). Indeed, other explanations could be proposed for these mood changes coinciding with hormone administration. As previously mentioned patients might have felt more positive after beginning hormone treatment due to their perceived progress towards SRS. Arguing against this, patients were tested after seeing their psychiatrist and were informed during consultation that hormonal treatment was soon to commence. This alone may make them more positive in these moods at time of first test session. However, in response to this, it might take a while for the news to have its impact and their physical feminisation by the time of their second test session, might have improved their mood too. Also, one

could put forward that those tested one day prior to SRS would either be more negative (anxiety or apprehension) or more positive (confident and composed), not due to hormonal withdrawal, but due to surgery pending. Alternatively a relief factor may be involved with the pre-surgical group. For example, composure and confidence increases when patients commence treatment, but remains the same when they are withdrawn from hormones. Therefore, it is difficult to know for certain to what degree the desire to begin living in the female gender role encouraged these changes in mood rather than the ERT. It is unethical to employ placebo-controlled trials using cross-sex hormones in M-F transsexuals in which the patients could remain blind. However, as no change in mood was observed in the pre-surgical group, a hormonal explanation is weak.

Demand characteristics might have also influenced the findings of the current study. This is particularly true in the area of sexual orientation. As outlined in Chapter 1, there have been reports that sexual orientation influences pattern of cognitive style (Gladue et al, 1990; Kimura, 1996; Hall and Kimura, 1995). There are many websites and literature available to transsexuals regarding the treatment process of SRS. Patients may have read misleading information from the experiences of other transsexuals who have transitioned, such as ways to 'successfully' present themselves to

consultants in order to proceed and progress through their treatment. Patients may have felt that they would have to report their sexual preference conducive to societal norms and so give information that they perceived the consultants wanted to hear. Whilst sexual orientation would not influence a consultant's decision in a patient's treatment, it is possible that the information collected in the present study is inaccurate. However, sexual orientation was not a major focus of the study and this problem would seem unlikely to influence findings in other areas, e.g., mood.

Another potential problem, particularly in the group awaiting hormone treatment, is difficulty guaranteeing their hormone status. It is impossible to dismiss the idea that there were any pre-intervention aspects of the patient's endocrine histories that might have been at work. One cannot assume they have not already been taking some form of hormone treatment unofficially obtained. If some of the group were, this could have obscured possible changes in cognitive performance and mood in those commencing treatment. However, this is less likely to have affected the pre-surgical group because they were already on hormones and were about to be withdrawn from hormones for medical reasons to avoid health complications during surgery.

Another problem may relate to relatively low doses of hormones given to those commencing hormone treatment. Some patients were taking therapeutic doses of hormones. Low dosages of cross-sex hormone, such as 20 mcg. Ethinyloestradiol are prescribed for some patients who are experiencing distress associated with Gender Identity Disorder. Based on clinical opinion this dose is prescribed to reduce these negative feelings rather than to feminise the body physically. This may explain why mood effects were observed in those commencing treatment and why dosages were not adequate to alter brain function in which performance in memory and cognition could be observed. Again, this would not have been a problem in the pre-surgical group who was on doses adequate for physical feminisation.

Some patients undergoing treatment with different hormones such as Androcur and Provera, as well as oestrogen, were included in this study. However, only small numbers of those taking these combinations of hormones were used. Thus, this study is unable to address questions as to whether the addition of these hormones alters relationships between oestrogen and behaviour (Zweifel and O'Brien, 1997). However, an analysis of data excluding participants taking hormones in addition to

oestrogen suggested that these few individuals did not distort the main findings of the current study.

It is possible that there was a confound between the two experimental groups (those patients commencing treatment versus pre-surgical patients) in terms of type of hormone treatment received. All those commencing treatment were taking ethinyloestradiol (synthetic oestrogen). Two patients in this group were taking Androcur in addition to this. In the pre-surgical group, patients were taking a wider range of hormones including Premarin (naturally conjugated equine oestrogen) (n = 18), Premarin with Provera (n = 1), Premarin with Androcur (n = 4) or ethinyloestradiol (n = 4). It is possible that the different hormone combinations in these groups may have impacted on the findings, such that the groups were not comparable in terms of hormone status to observe reciprocal changes between groups in memory, cognition and mood. However, in general, results for the two groups were similar, despite the fact that they were taking different preparations of oestrogen. This possibly suggests that neither type of oestrogen influences most of the outcomes. However, for some outcome measures the two groups differed. Specifically, Digit Span scores improved in patients commencing treatment (group 1). Further, composure and confidence were also enhanced in this group, whereas there was no change

in Digit Span or composure and confidence in patients withdrawing from hormone treatment (group 2). Further, Object memory deteriorated and Visual PAL improved in patients withdrawing from hormone treatment (group 2), whereas no change in performance for Object memory and Visual PAL was seen in patients commencing treatment (group 1). One possible explanation for these variations could be the differences in specific hormones taken between the two groups.

It is also useful to compare the hormones used in the current study to those used in other studies, where more patients received anti-androgens which were of a higher dosage than those taken by the group commencing treatment in the present study (Van Goozen et al, 1995; Slabbekoorn et al, 1998). Further recent findings by these researchers (Van Goozen et al, 2002) did not replicate their previous findings of an activational effect of hormones on visual-spatial ability in M-F transsexuals (Van Goozen et al, 1995). In addition to anti-androgens, the patients in this more recent study were given either oestradiol patches or ethinyloestradiol. Possible explanations that could reconcile the findings among these sets of data include differing dosages and type of hormone used.

4.6. Summary

This study examined whether the suppression of testosterone combined with the administration of cross-sex hormones led to changes in memory, cognition and mood in M-F transsexuals commencing treatment. A further question was whether withdrawal of cross-sex hormones prior to surgery led to changes in memory, cognition and mood. Patients commencing treatment, improved on a test of concentration and mood enhancements in composure and confidence, whereas patients withdrawing from hormones showed an improvement in Visual PAL scores and a decline in Object memory. No clear hormone effects on cognition, memory and mood were observed where onset of oestrogen treatment had one effect coinciding with a corresponding effect of oestrogen withdrawal. Withdrawal of hormone treatment did not coincide with a decline in DS scores or changes in composure and confidence. Further, commencement of hormone treatment did not coincide with a decline in Visual PAL and an improvement in Object memory. It is probable that the results may not be a hormone effect. Earlier findings from Chapter 2 were not replicated and manipulations of sex hormones appear to be unrelated to performance on the other sexually dimorphic measures. Therefore results are far from conclusive as to whether hormonal influences on memory and cognition are restricted to

tasks that show sex differences, particularly as past research shows that DS does not show a sex difference. The tighter control in the present study of potential confounding factors of age, Vocabulary, hand preference, education and sexual orientation point towards the interpretation of chance findings in Chapter 2 that was unreliable. Results do not support an oestrogenic enhancement of tasks that show sex differences, suggesting that as with Chapter 2 ameliorating influences of oestrogen observed in women may apply to men as well. However, there are clearly other methodological factors which cannot be controlled for which have led to inconsistent findings.

CHAPTER 5: CONCLUSIONS

5.1. Hypotheses

In the first, second and third studies (Chapters 2, 3 and 4, respectively), three main hypotheses were investigated. The first of these predicted that M-F transsexuals who were administered oestrogen and other cross-sex hormones as treatment, would perform better than those awaiting treatment on memory and cognitive tasks favouring females. Conversely they would perform worse than those awaiting treatment on tasks favouring males.

Partial support was found for this hypothesis in the first study (Chapter 2). M-F transsexuals taking oestrogen and/or other cross-sex hormones were better than M-F transsexuals awaiting such treatment on a memory task that showed a sex difference favouring females, Verbal Paired Associate Learning (Verbal PAL) (see Figure 12). As predicted these two groups performed similarly on a memory and a cognitive task that show no sex difference (Digit Span and Vocabulary). An activating influence of hormones on other cognitive tasks that generally show large sex differences was not found however, as performance on Mental Rotations and

Controlled Associations did not differ between groups. There was no difference between groups in mood. See Table 31 for a summary of findings from Chapter 2.

Table 31: Summary of findings from study 1 (Chapter 2)

FIRST STUDY (Chapter 2)	N	DESIGN	TESTS USED	DURATION AND DOSAGE OF HORMONE TREATMENT	FINDINGS
	59 M-F transsexual patients. Those awaiting hormone treatment = 30. Those on hormone treatment = 29.	Between Subjects.	<ul style="list-style-type: none"> *Verbal Paired Associate Learning (Verbal PAL) (WMS) *Digit Span (DS) (WMS) *Mental Rotations (MR) (Vandenberg and Kuse (1987)) *Controlled Associations *Vocabulary (Vandenberg and Kuse (1987)) *Profile of Mood States (POMS) (Lorr and McNair- 1988) 	<p>Patients were treated with Premarin (n = 27) and ethinyloestradiol (n = 2). Some patients on Premarin were also receiving Provera (medroxyprogesterone acetate) (n = 3) or Androcur (n = 5). For patients receiving Premarin, dosages ranged from 2.5 to 7.5 mgs (milligrams), daily. Dosage of Provera was 5 mgs, daily and those patients taking ethinyloestradiol received 50 mcgs (micrograms), daily. Duration of treatment ranged from 3 to 72 months.</p>	<p>No differences were seen between groups on DS, MR, Vocabulary or Controlled Associations.</p> <p>Those taking hormones performed better than those not taking hormones on Verbal PAL.</p> <p>Duration and dosage of hormone treatment was not associated with scores on the memory or cognitive measures.</p> <p>Mood did not differ between the 2 groups.</p>

The second study (Chapter 3) evaluated past research to assess whether the tasks used in research on oestrogen and memory show reliable and substantial sex differences. Findings from this meta-analysis clearly showed small ESs for the tasks used and large variability among studies. The present review indicates that certain tests show sex differences favouring either females or males, however the fail safe findings (Rosenthal, 1979) place reliability of these findings in jeopardy. This means that the number of studies that would be needed to reverse the conclusion of a significant sex difference on the memory tests reviewed was often relatively small. The available data suggest that there are medium sex differences favouring females on Location memory only and no medium or larger sex differences favouring males or females on any other test. The remaining tests appear to show small to negligible sex differences (See Figure 12).

For each study in this review, characteristics of sample size, age of participants, year of publication, source of study and type of participant were collected. This was done to determine whether such characteristics influenced the magnitude of sex difference. Age was identified as a potential factor to influence ES for sex differences in Visual Reproduction (VR) and Logical Memory (LM), although more research would be needed

to confirm these age and memory performance relationships (see Figure 12). Year of publication was positively associated with LM (immediate recall), however when this relationship was examined by use of a scatterplot, this association does not suggest that as year of publication increases so does the sex difference. It appears that during the late 1980s the sex difference marginally favours males. The sex difference reduces around the mid to late 1990s then the picture becomes more complex in the following years. Up to 2002, sex differences among studies do not consistently favour either males or females. See Table 32 for a summary of findings in past studies.

The findings from the meta-analysis possibly indicate there are other independent factors among studies contributing to sex differences in performance. Other factors such as sexual orientation, handedness and mood of participants may explain some of the inconsistencies in past research examining sex differences in memory, however such information was not available consistently in the studies used in this review. These factors might explain the large variability in ESs obtained for these memory tasks. As it is hypothesised that only those tasks that show sex differences are influenced by sex hormones and that the magnitude of sex differences may be influenced by other factors than hormones, it might be

helpful to control for factors like mood, handedness and sexual orientation. Failure to control for such factors might contribute to failure to find oestrogenic effects on memory and cognition, even when using tasks that are thought to show sex differences. See Table 32 for a summary of findings in studies of sex differences in selected memory tasks.

Table 32: Summary of findings from study 2 (Chapter 3)

TESTS SELECTED FOR REVIEW	N †	ES / weighted ES	Magnitude of ES	FACTORS INFLUENCING SEX						Homogeneity achieved	sex difference
				Age	Type of sample	Sample size	Whether published or not	Year of publication			
Object memory	13	.26/.26	small	ns	ns	ns	ns	ns	ns	no	yes
Location memory	18	.53/.44	medium	ns	ns	ns	ns	-tive Ω	ns	no	yes
Verbal PAL (composite)	19	.21/.20	very small	ns	δ	-tive Ω	δ	ns	ns	yes	yes
Verbal PAL (immediate recall)	6	.12/.30	negligible	ns	δ	ns	ns	ns	ns	no	no
Verbal PAL (delayed recall)	5	.07/.06	negligible	ns	δ	ns	ns	ns	ns	yes	no
DS	34	-.01/.02	negligible	ns	ns	ns	ns	ns	ns	no	no
Corsi Spatial Span	9	-.20/-.29	small	ns	ns	ns	ns	ns	ns	no	yes
LM (composite)	16	.00/-.11	negligible	+tive Ω	δ	ns	δ	ns	ns	no	no
LM (immediate recall)	24	.13/.00	negligible	ns	ns	ns	ns	+tive Ω	ns	no	no
LM (delayed recall)	20	.09/-.11	negligible	ns	ns	ns	ns	ns	ns	no	no
VR (composite)	11	-.27/-.23	small	+tive Ω	δ	ns	δ	ns	ns	no	yes
VR (immediate recall)	19	-.19/-.11	negligible	ns	ns	ns	ns	ns	ns	no	no
VR (delayed recall)	14	-.07-.17	negligible	ns	ns	ns	\Leftarrow	ns	ns	no	no

† ESs of .20, .50 and .80 indicate small, medium, and large effects, respectively, and this criterion was used to assess the magnitude of sex differences. ESs of .15 - .19 were interpreted as very small, and ESs below .15 were interpreted as negligible.

δ Cannot be computed because this variable is constant.

\Leftarrow Cannot be computed, as the uneven splits of the categories do not fulfill the assumption required for statistical analysis. i.e., 10% in one category versus 90% in the other (Tabachnik and Fidell, 1996).

Ω +tive = positive correlation; Ω -tive – negative correlation

The third study (Chapter 4) was carried out to assess the reliability of findings from study 1 regarding Verbal PAL (Chapter 2). An influence of oestrogen on Verbal PAL performance was not replicated in the third study (Chapter 4), using a different and larger group of M-F transsexuals. This study employed between group analyses and a more powerful design, where the same individuals were tested before then after commencing hormone treatment. A subgroup of patients was also tested when established on hormone treatment and then during withdrawal of hormone treatment. Some changes in memory and cognition were observed however.

Findings suggested that changes in memory and cognition associated with oestrogen treatment or treatment with other cross-sex hormones may not be restricted solely to tasks showing sex differences. Firstly, withdrawal of hormone treatment led to deterioration in a task favouring females (Object memory), and improvement on a visual memory task hypothesised to favour males (Visual PAL) (see Figure 12) (i.e., in both cases, movement toward a more male-typical pattern of performance). Secondly, short-term hormone administration led to an enhancement on a test of concentration (DS), a test that is not sexually dimorphic. Thirdly, an improvement in mood was observed after short-term administration of hormones. However, it is important to remember that these findings may be due to chance and

not due to a hormonal effect on memory, cognition and mood. Chapter 4 discusses alternative explanations for these observed changes. See Table 33 for a summary of these findings.

Table 33: Summary of findings from the third study (Chapter 4)

	N	DESIGN	TESTS USED	DURATION AND DOSAGE OF HORMONE TREATMENT	FINDINGS
Third study (Chapter 4): Analysis 1.	103 M-F transsexual patients. 63 M-F transsexuals on hormone treatment versus 40 M-F transsexuals off hormones treatment.	Between Subjects	<p>The following battery of tests was administered for all subjects across analyses 1-4.</p> <ul style="list-style-type: none"> *The Profile Of Mood States (POMS) - (Lorr and McNair, 1988). *Handedness *Figural memory (Wechsler Memory Scale - Revised) (WMS - R). *Logical Memory (LM) (WMS, 1945) *Visual PAL (WMS - R). *Verbal PAL (WMS, 1945). *Visual Reproduction (VR) (WMS). *Digit Span (DS) (WMS - R). *Visual Memory Span (WMS - R). *Judgement of Line Orientation (JOLO) (Collaer, 1992). *FAS - Verbal Fluency (Benton and Hamsher, 1983) *Mental Rotations (Vandenberg and Kuse, 1987). *Controlled Associations (Ekstrom, French and Harman, 1976). *Object and Location memory (Silverman and Eals, 1992). *Vocabulary (Ekstrom, French and Harman, 1976). *Demographic Information 	<p><u>Analysis 1.</u></p> <p>Premarin (n = 32), ethinyloestradiol (n = 18), Androcur and ethinyloestradiol (n = 4), Premarin and Androcur (n = 6), Premarin and Provera (n = 3). Dosage of Premarin ranged from 1.25 to 7.5 mgs (milligrams), daily. Dosage of Provera was 5-15 mgs, daily. Dosage of Androcur was 100-150 mcgs (micrograms). Dosage of ethinyloestradiol was 10-100 mcgs, daily. Duration of hormone treatment ranged from 4 to 156 months.</p>	<p><u>Analysis 1.</u></p> <p><u>Participant characteristics:</u> Those taking hormone treatment were older, more confident and more composed. Differences in educational background, Vocabulary, sexual orientation, handedness and the other 4 moods were non-significant.</p> <p><u>Memory and cognitive measures:</u> There were no differences between groups on any of the memory or cognitive measures.</p> <p><u>Duration of treatment:</u> This was not associated with scores on the memory or cognitive measures.</p> <p><u>Dosage of treatment:</u> This was correlated positively with JOLO scores.</p>

Table 33 continued

	N	DESIGN	TESTS USED	DURATION AND DOSAGE OF HORMONE	FINDINGS
<p>Treatment with oestrogen only.</p>	<p>90 M-F transsexual patients. 50 M-F transsexual patients on oestrogen only treatment versus 40 M-F transsexuals off hormone treatment.</p>	<p>Between Subjects.</p>	<p>Same as above</p>	<p><u>Oestrogen only.</u> Premarin (n = 32) and ethinyloestradiol (n = 18). Dosage of Premarin ranged from 1.25 to 7.5 mgs (milligrams), daily. Dosage of ethinyloestradiol was 10-100 mcgs, daily. Duration of treatment ranged from 4 to 120 months.</p>	<p><u>Oestrogen only.</u> <u>Participant characteristics:</u> Those taking hormone treatment were older, more confident, more composed and more clearheaded. Differences in educational background, Vocabulary, sexual orientation, handedness and the other 3 moods were non-significant. <u>Memory and cognitive measures:</u> There were no differences between groups on any of the memory or cognitive measures. <u>Duration of treatment:</u> Length of treatment correlated positively with Visual Span Backwards and JOLO (Total correct). <u>Dosage of treatment:</u> Dosage of treatment correlated positively with Digit Span Backwards, JOLO and LM (delayed recall). Treatment with Androcur or Provera: To examine whether the addition of Provera to oestrogen influenced results, those taking oestrogen with Androcur were excluded from this analysis (n = 10). Group differences in three moods remained. To examine whether the addition of Androcur to oestrogen influenced results, those taking Provera in addition to oestrogen were excluded. The Group differences remained in composure and confidence, but did not remain for clearheaded. For both of these analyses between group differences in memory and cognition remained non-significant.</p>

Table 33 continued

	N	DESIGN	TESTS USED	DURATION AND DOSAGE OF HORMONE TREATMENT	FINDINGS
Analysis 2. Matched groups.	68 M-F transsexual patients. 34 M-F transsexuals on hormone treatment versus 34 M-F transsexuals off hormones treatment	Between Subjects.	Same as above	<u>Analysis 2.</u> Premarin (n = 15) and ethinyloestradiol (n = 9), Androcur and ethinyloestradiol (n = 4), Premarin and Androcur (n = 4), Premarin and Provera (n = 2). Dosage of Premarin ranged from 1.25 to 7.5 mgs (milligrams), daily. Dosage of Provera was 5-15 mgs, daily. Dosage of Androcur was 100-150 mcgs (micrograms). Dosage of ethinyloestradiol was 50-100 mcgs, daily. Duration of hormones ranged from 4 to 156 months.	<u>Analysis 2.</u> <u>Participant characteristics:</u> Those taking hormone treatment were older, more confident, more composed and more clearheaded. Differences in educational background, Vocabulary, sexual orientation, handedness and the other 3 moods were non-significant. <u>Memory and cognitive measures:</u> Results of the ANCOVA using mood as a covariate indicated that there were no significant differences between those taking hormones and those not taking hormones on any of the memory or cognitive measures. <u>Duration of treatment:</u> Length of treatment correlated negatively with Object memory. <u>Dosage of treatment:</u> This was not associated with scores on the memory or cognitive measures.

Table 33 continued

	N	DESIGN	TESTS USED	DURATION AND DOSAGE OF HORMONE TREATMENT	FINDINGS
Analysis 3.	54 M-F transsexuals	2 x 2 mixed factors: Within Subjects factor - HORMONE (on versus off) and Between subjects factor - GROUP (those commencing hormone treatment versus those withdrawing from hormone treatment).	Same as above	<p><u>Analysis 3.</u></p> <p>Premarin (n = 18), ethinyloestradiol (n = 29), Androcur and ethinyloestradiol (n = 2), Premarin and Androcur (n = 4), Premarin and Provera (n = 1). Dosage of Premarin ranged from 1.25 to 7.5 mgs (milligrams), daily. Dosage of Provera was 15 mgs, daily. Dosage of Androcur was 50-100 mcgs (micrograms). Dosage of ethinyloestradiol was 10-150 mcgs, daily. Duration of hormone ranged from 3 to 156 months.</p>	<p><u>Analysis 3.</u></p> <p><u>Participant characteristics:</u> Those taking hormones were more composed than when they were not taking hormones. Differences in age, educational background, Vocabulary, sexual orientation, handedness and the other moods were non-significant.</p> <p><u>Memory and cognitive measures:</u> Those taking hormones had higher DS Backward scores than when they were not taking hormones. Those taking hormones had lower Visual PAL, trial 1 scores than when they were not taking hormones. Patients in the commencing hormone treatment group scored higher on LM (delayed recall) than those in the group withdrawing from treatment. There were significant interactions between GROUP and HORMONE for Visual PAL, trial 1, Visual PAL, trials 1-3 and Object memory. Those commencing treatment did not differ on these measures from time 1 to 2, however pre-surgical patients did differ on these measures from time 1 to 2. See analysis 4 (below) for an interpretation of these findings.</p> <p><u>Duration of treatment:</u> Length of treatment correlated negatively with LM.</p> <p><u>Dosage of treatment:</u> Dosage of treatment correlated positively with JOLO scores.</p>

Table 33 continued

N	DESIGN	TESTS USED	DURATION AND DOSAGE OF HORMONE TREATMENT	FINDINGS
Analysis 4. (group 1). 27 M-F transsexuals	Repeated measures. Patients tested before and then during hormone treatment.	Same as above	<u>Analysis 4.</u> Ethinyloestradiol (n = 25), Androcur and ethinyloestradiol (n = 2). Dosage of Androcur was 50-100 mcgs (micrograms). Dosage of ethinyloestradiol was 10-100 mcgs, daily. Duration of hormone treatment ranged from 3 to 14 months.	<u>Analysis 4.</u> <u>Participant characteristics:</u> Those taking hormones were more composed and confident than when they were not taking hormones. Within group differences in educational background, Vocabulary, sexual orientation, handedness and the other moods were non-significant. Memory and cognitive measures: Those taking hormones had higher DS Backward scores than when they were not taking hormones. <u>Duration of treatment:</u> This was not associated with scores on the memory or cognitive measures. <u>Dosage of treatment:</u> Dosage of treatment correlated positively with LM, Mental Rotations, Controlled Associations and how elated and energetic patients felt.

Table 33 continued

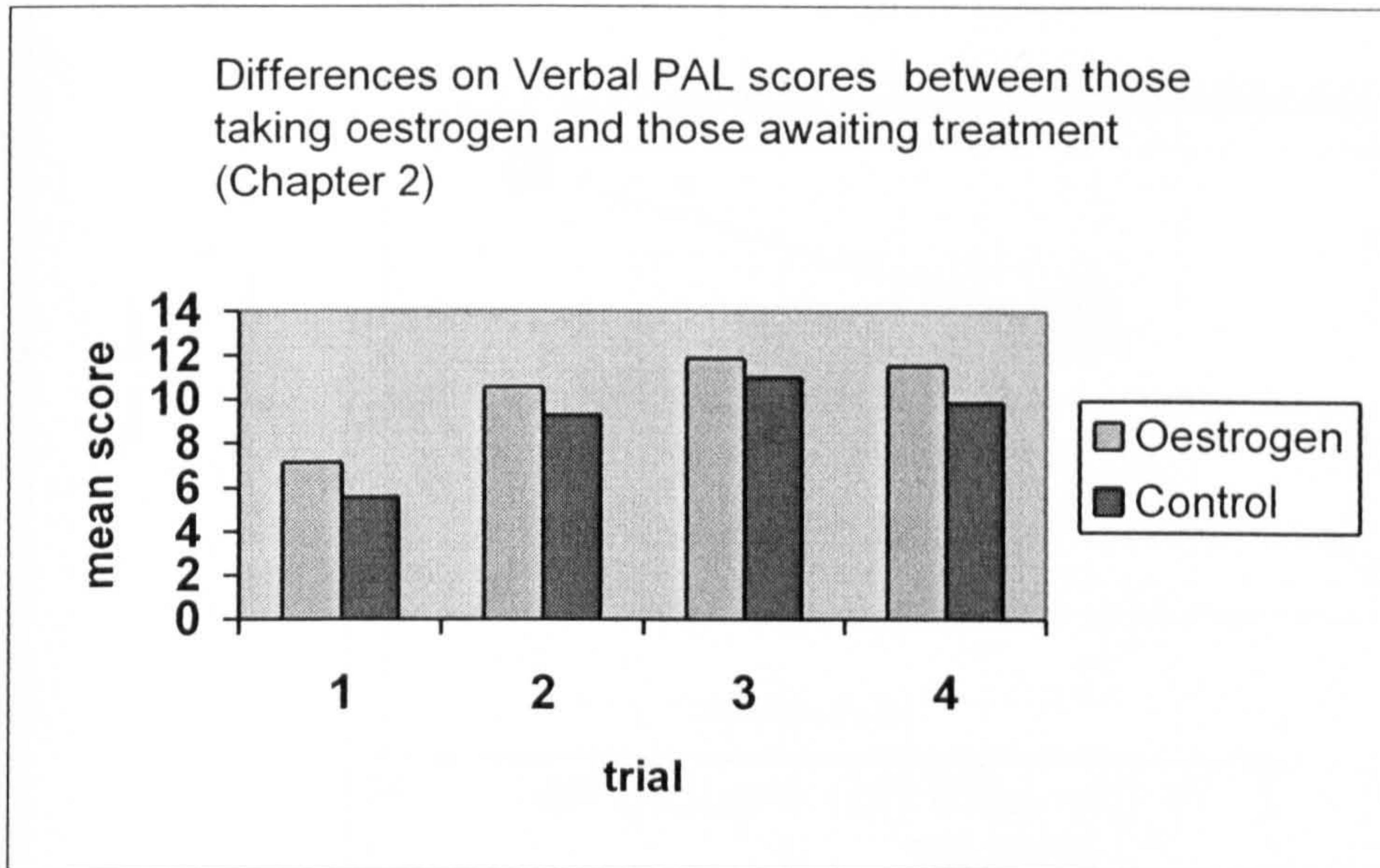
	N	DESIGN	TESTS USED	DURATION AND DOSAGE OF HORMONE TREATMENT	FINDINGS
Analysis 4. (group 2).	27 M-F transsexuals	Repeated measures. Patients tested during treatment and then when withdrawn for 8 weeks.	Same as above	<p><u>Analysis 4.</u></p> <p>Premarin (n = 18), ethinyloestradiol (n = 4), Androcur and Premarin (n = 4), Premarin and Provera (n = 1). Dosage of Premarin ranged from 1.25 to 7.5 mgs (milligrams), daily. Dosage of Provera was 15 mgs, daily. Dosage of Androcur was 50-100 mcgs (micrograms). Dosage of ethinyloestradiol was 100-150 mcgs, daily. Dosage of hormone treatment ranged from 17 to 156 months.</p>	<p><u>Analysis 4.</u></p> <p><u>Participant characteristics:</u> Within group differences in mood, educational background, Vocabulary, sexual orientation, handedness and the other moods were non-significant.</p> <p><u>Memory and cognitive measures:</u> Those taking hormones had better Object memory scores than when they were withdrawn from hormone treatment. Visual PAL, trial 1 and Visual PAL (immediate recall) scores improved when patients were withdrawn from hormone therapy.</p> <p><u>Duration of treatment:</u> Length of treatment correlated positively with Visual PAL, trial 2 and Visual PAL (immediate recall).</p> <p><u>Dosage of treatment:</u> This was not associated with scores on the memory or cognitive measures.</p>

Table 33 continued

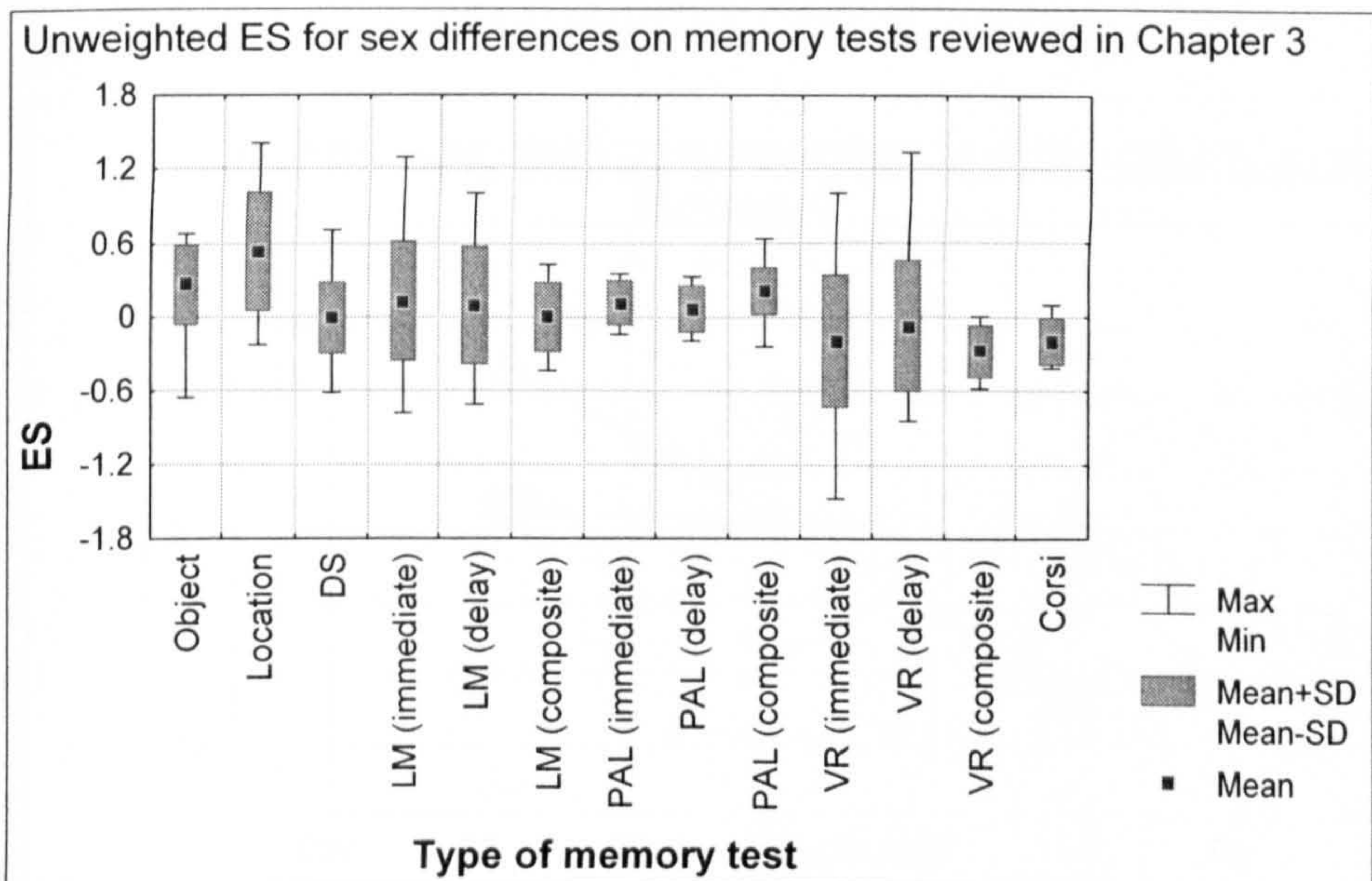
N	DESIGN	TESTS USED	DURATION AND DOSAGE OF HORMONE TREATMENT	FINDINGS
Analysis 4 (group 3). Control group.	20 M-F transsexuals	Repeated measures. Patients tested twice, both times during hormone treatment	<p>Analysis 4.</p> <p>Premarin (n = 5), ethinyloestradiol (n = 12), Premarin and Provera (n = 1), Ethinyloestradiol and Androcur (n = 2). Dosage of Premarin ranged from 5 to 7.5 mgs (milligrams), daily. Dosage of Provera was 15 mgs, daily. Dosage of Androcur was 100-150 mcgs (micrograms). Dosage of ethinyloestradiol was 50-150 mcgs, daily. Duration of hormone treatment ranged from 4 to 88 months.</p>	<p>Analysis 4.</p> <p><u>Participant characteristics:</u> Within group differences in mood, educational background, Vocabulary, sexual orientation, handedness and the other moods were non-significant.</p> <p><u>Memory and cognitive measures:</u> At second test session, score on LM scores and Figural memory scores improved, indicating possible practice effects.</p> <p><u>Duration of treatment:</u> Length of treatment correlated positively with Visual memory span (backward and total) scores and Visual PAL, trials 1-3 (immediate recall).</p> <p><u>Dosage of treatment:</u> This was not associated with scores on the memory or cognitive measures.</p>

Figure 12: Graphical summaries of main findings from Chapters 2, 3 and 4.

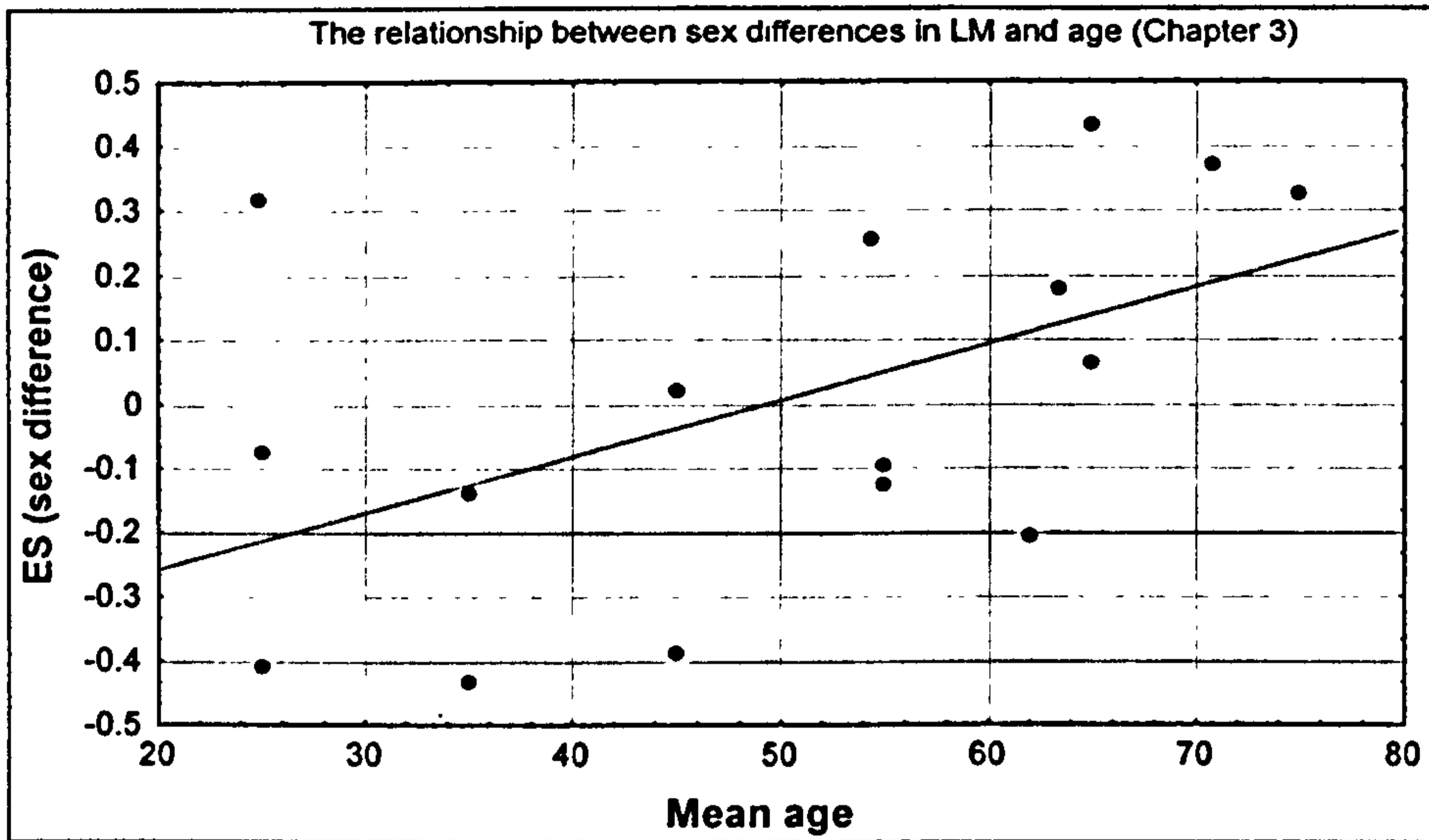
12a)



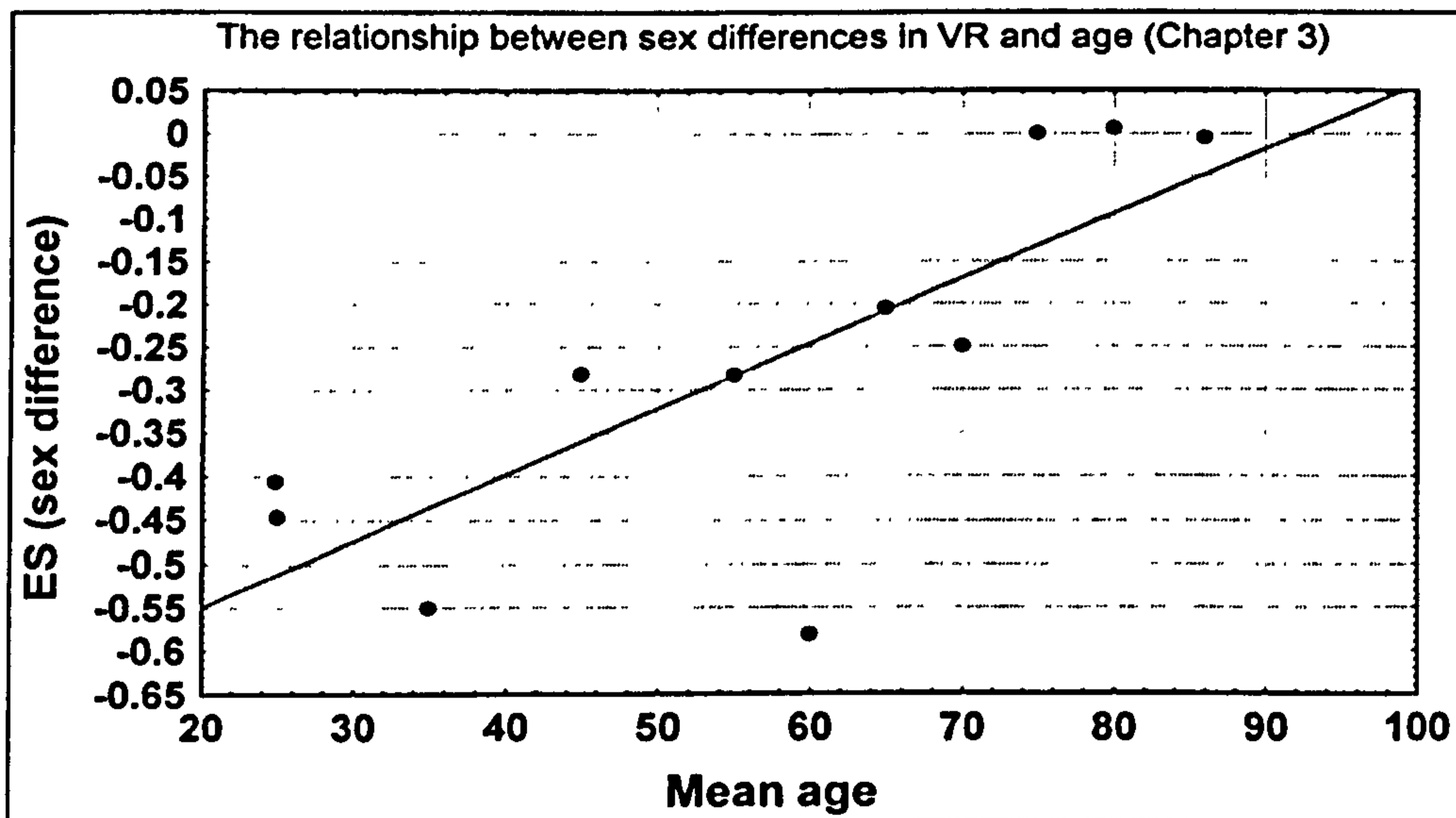
12b)



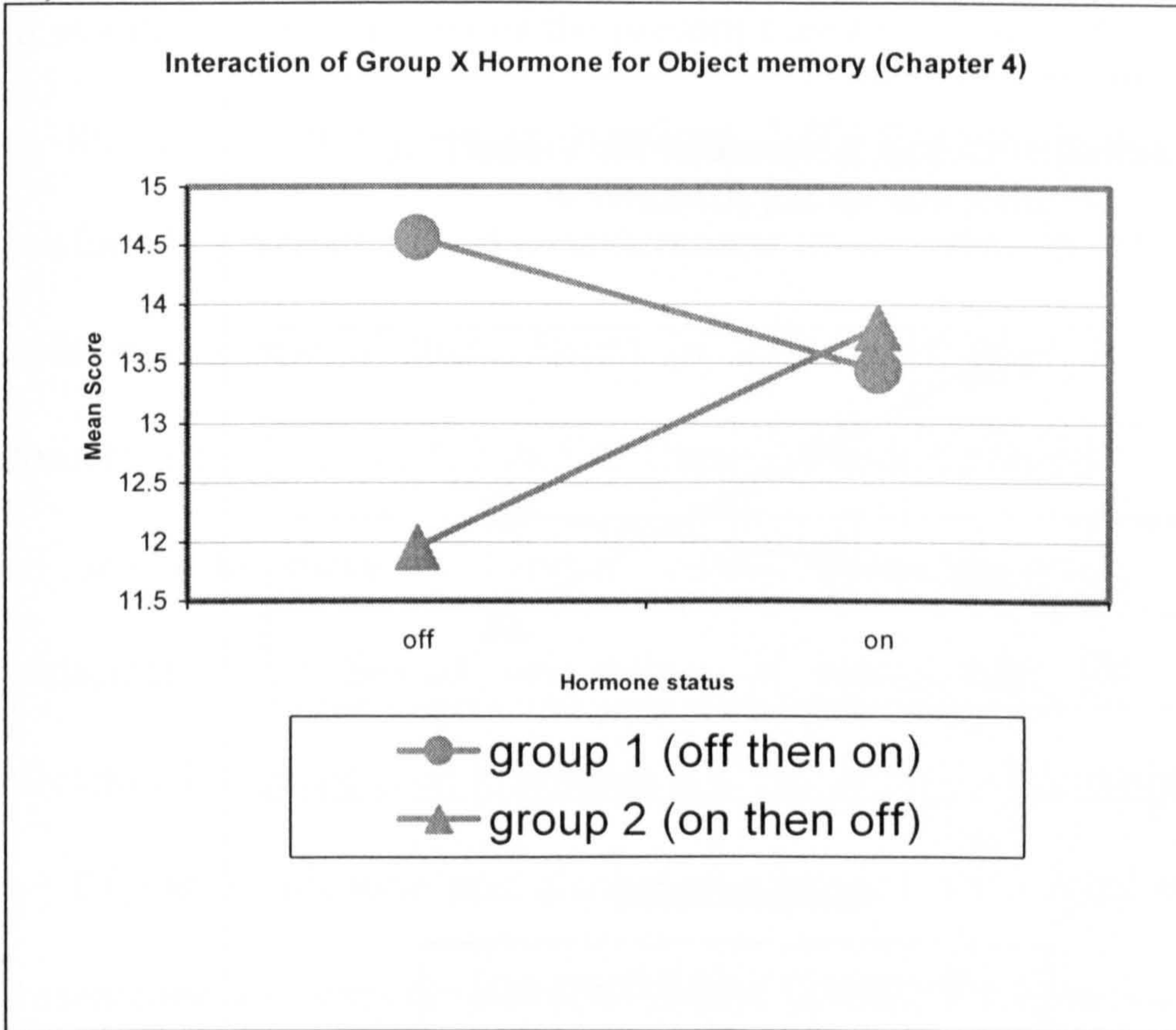
12c)



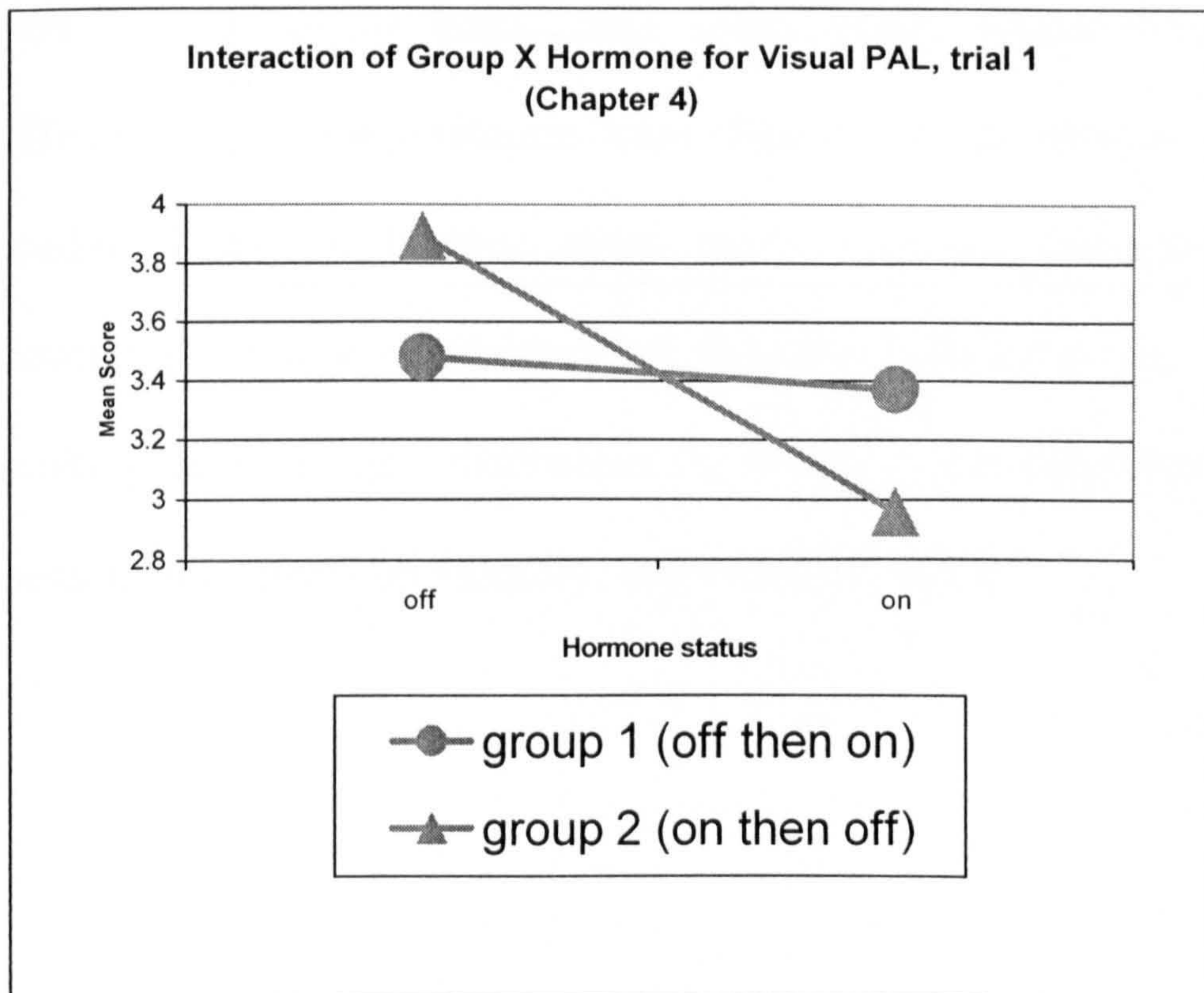
12d)



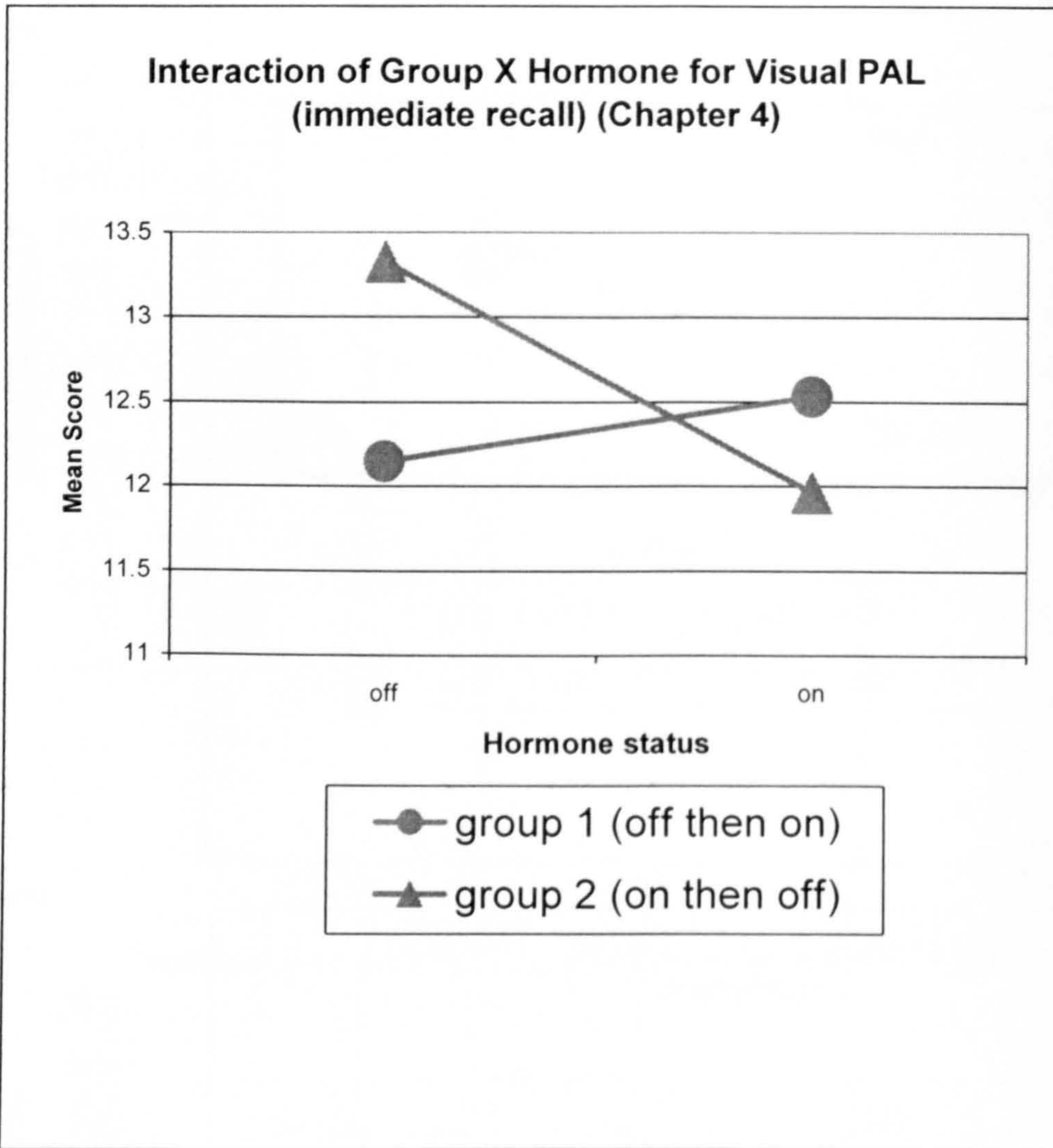
12e)



12f)



12g)



5.2. Issues relating to the present thesis

In evaluating the findings of the present thesis it is useful now to refer back to the introductory chapter (sections 1.10 through to 1.18) regarding confounding variables and considerations in sex research. The next section addresses a few of these issues in light of findings from the studies described in Chapters 2, 3 and 4. These issues are also relevant to research on sex differences in general. Issues discussed involve: i) Age of participants; ii) Sexual orientation of participants; iii) Diurnal and circannual influences on hormones and on memory and cognitive abilities; iv) Effects of nicotine and alcohol on memory and cognition; v) Sex of Researcher and experimenter/participant biases; vi) Situational variables, and vii) Publication bias. These issues might explain why no reliable effects of hormone treatment were observed in the samples employed in studies 1 and 3. Further, these issues may aid interpretation of the confusing mixture of positive and negative findings among other studies looking at both sex differences in memory and cognition, as well as oestrogenic effects on memory, cognition and mood.

5.2.1. Age of participants

Cognitive and memory functions change with age (Bromley, 1958; Gilbert and Levee, 1971), therefore it was of concern in the first and third studies whether age influenced performance on memory and cognitive tasks. Age was not associated with memory or cognitive performance in the transsexual group from the first study (Chapter 2). For the third study (Chapter 4) however, significant positive associations were found between age and Vocabulary. Vocabulary scores increased with age. Conversely, Visual PAL scores decreased with age. Negative associations between other PAL tasks and age have also been reported (Gilbert and Levee, 1971). Where appropriate, ANCOVAs were used to control the influence of age on the memory and cognitive scores.

Age also influenced the magnitude of sex differences on some of the memory tasks included in the meta-analytic review (Study 2, Chapter 3). Past research has implicated age as a confounding factor in sex difference research (Drachman, 1976; Botwinick, 1977). In study 2, complex positive associations of age with LM and VR scores were found (See Figure 12). For LM, sex differences favoured males between the approximate ages of

20 and 40 years. The sex difference then reduces at approximately 50-60 years. In the following years up to the late 70s, the sex difference gradually reverses to favour females. For VR, ES favours males, with the sex difference decreasing with age, to near zero. Due to the small numbers of studies collected for the meta-analysis, further studies would be needed to support these findings, however the present research confirms that age is influential. Thus, it is necessary to control for age in research looking into sex differences in memory and cognition.

5.2.2. Sexual Orientation

As previously mentioned, prenatal hormones are hypothesised to affect sexual orientation in humans (Adkins-Regan, 1988), which may also be associated with a different pattern of cognitive sex differences. For example male homosexuals are more similar to female heterosexuals, than male heterosexuals, in cognitive pattern. Further, female homosexuals are more similar to male heterosexuals, than female heterosexuals, in cognitive pattern. It is further suggested that homosexual transsexuals differ from non-homosexual transsexuals in cognitive pattern due to atypical prenatal hormone exposure. Spatial performance of these transsexuals was somewhere between males and females and in the direction of the other

sex. Homosexual transsexuals were not susceptible to activating effects of cross-sex hormones on spatial ability seen in previous research that involved homosexual and heterosexual transsexuals (Van Goozen et al, 2002; Slabbekoorn et al, 1999; Van Goozen et al, 1995).

These hypotheses could not be tested in the first study (Chapter 2), as data on sexual orientation of the patients was not collected. Therefore, sexual orientation cannot be ruled out as a confounding influence on the memory and cognitive scores from this study. In the third study however (Chapter 4), data on sexual orientation of patients was collected. There were no differences between those patients taking hormones and those not taking hormones in the frequency of types of sexuality reported. Further, the repeated measures analyses eliminated sexual orientation as a confounding influence on memory and cognitive scores.

Chapter 4 discusses how data collected regarding the sexual orientation of patients may be biased by demand characteristics. For example, given the strong heterosexual bias in our culture, the patients may have reported a sexual orientation conducive to societal norms, such as a heterosexual orientation when in fact the patient was homosexual. Alternatively, the patients may have reported a sexual orientation that they thought would

portray them as more cross-gendered, such as a homosexual orientation when in fact the patient was heterosexual. If self-reported sexual orientation of the patients in the third study (Chapter 4) was biased, there might have been more or fewer homosexuals in this sample than thought. The validity of self reported sexual orientation is not only a problem for the present research, but also applies to other research in this area of hormonal effects of cross-sex hormones in transsexual populations.

As sexual orientation may relate to cognitive abilities that show sex differences (Gladue, Beatty, Larson and Staton, 1990; Kimura, 1996; Hall and Kimura, 1995; Sanders and Wright, 1997; Wegesin, 1998; Neave, Menaged and Weightman, 1999), the present study cannot completely rule out the possibility that differences in sexual orientation are distorting relationships between hormones and memory or cognition. For example, a recent study examined homosexual M-F transsexuals only, before and during their hormone treatment (Van Goozen et al, 2002). Using visual-spatial tasks that show sex differences, these researchers found possible organising effects in these M-F transsexuals, such that their mean scores were positioned between the male and female controls. However, no activational effects of hormone treatment were found. The authors suggest that these homosexual transsexuals may be seen as intersexual as their

cognitive performance was different to that of biological males, yet also different to biological females. It was concluded that homosexual M-F transsexuals were not predisposed to activating effects of cross-sex hormones. In contrast, when these researchers employed a sample of M-F transsexuals with mixed sexualities, activational effects were observed after 3 months of hormone treatment (Van Goozen et al, 1995). Their findings suggest that if the transsexuals employed in study 3 were predominantly homosexual, the results obtained would be non-significant, such that activational effects of hormones on memory and cognition would not be seen. However, as described previously, there were changes in memory and cognition that coincided with hormone treatment. Therefore, the initial findings may be spurious and need to be replicated.

A final concern regarding sexual orientation and its influence on sexually-dimorphic memory and cognitive tasks involves measurement of sexual orientation. The present study crudely classified transsexuals into one of four categories (heterosexual, homosexual, bisexual or asexual). It is argued that a person's sexual orientation cannot be classified into discrete categories. Rather, sexuality should be viewed as lying on a continuum, somewhere between homosexuality and heterosexuality (Kinsey, Pomeroy and Martin, 1948). Conceptualisations of sexual orientation vary among

researchers. As there is a discrepancy between a person's attitude and their actual behaviour (Ajzen and Fishbein, 1975), the two most common aspects of sexual orientation are sexual behaviour and sexual fantasies. In the present study (Chapter 4), it is unclear from the basic categories used to classify sexual orientation whether the patients' self-assigned sexual orientation was from a behavioural or a psychological viewpoint. It is certainly possible that sexual fantasies of transsexuals may be incongruent to their sexual behaviour. Further Klein, Sepekoff and Wolf (1985), developed the Klein Sexual Orientation Grid (KSOG). This assesses seven dimensions including sexual attraction, sexual behaviour, sexual fantasies, emotional preference, social preference, self-identification and heterosexual/homosexual life-style. It is argued that valid data regarding a person's sexual orientation can only be collected using a detailed assessment like the KSOG. It is possible that if the patients from Chapter 4 had been assessed in this way, proportions of sexual orientations may have differed considerably from data originally collected. Furthermore, other researchers using sexual orientation for similar purposes, including those finding links to cognition, have typically used similarly crude categories. More research is needed into sexual orientation and cognitive pattern.

Problems of reliability and validity with self-reported sexual orientation might also be important in the present meta-analysis (Chapter 3). Sexual orientation is largely disregarded in sex difference research. None of the studies included in the meta-analysis reported sexual orientation of participants. This may be because it was a variable that was not considered important and therefore overlooked. Also, it might have been analysed but not reported due to non-significant findings, although this is less likely. Sexual orientation might be a factor that contributed to the large variability in the magnitude of sex differences in the memory tests reported in the second study. Some of the variability in the magnitude of sex differences in memory tasks might be explained if researchers considered sexual orientation as a possible confounding variable when studying sex differences. Finally, researchers rarely consider sexual orientation in their studies looking at hormonal influences on memory and cognition. Sexual orientation is not the major focus of the present research and was used as one of many background factors that could influence results.

5.2.3. Diurnal and circannual influences on memory and cognition

As previously outlined in Chapter 1, there is evidence, albeit inconsistent, suggesting that cognitive abilities that show sex differences are reported to

vary at different times of the day and different time of the year. (Sanders et al, 2002; Moffat and Hampson, 1996; Kimura, 1991; Wisniewski and Nelson, 2000). Due to the appointment intervals of patients tested in studies 1 and 3, it is important to state that patients were not tested at the same time of day or year and this may have added error variance to measurements. This also may be relevant to results of studies used in the present meta-analysis (Chapter 3) and in other repeated measures studies in neuroendocrinological research.

5.2.4. Effects of nicotine and alcohol on cognitive performance

Chapter 1 outlines research suggesting beneficial effects of nicotine on cognitive performance (Mangan, 1983; Rusted et al, 1995; Warburton and Arnall, 1994). The consultant psychiatrists advised the patients included in studies 1 and 3 that smoking is incompatible with hormone treatment, however it is difficult to know whether nicotine intake influenced the results in these studies, particularly as patients may not choose to follow such advice. Also, when researching hormonal effects or sex differences in memory and cognitive performance, nicotine intake of participants is rarely measured. Further research on the influences of nicotine on memory, cognition and mood would be helpful.

Alcohol consumption by participants in endocrine and cognitive research is largely ignored and is also difficult to control. Also, when researching sex differences in memory and cognitive performance, alcohol intake of participants is rarely assessed. However researchers have found that moderate alcohol intake leads to elevated hormone levels in women. Further, chronic moderate alcohol intake may be associated with delayed menopause (Gill, 2000). Therefore, in the present research, regular alcohol use may influence hormone levels and so influence the patients' memory, cognition or mood, even if they were tested sober during sessions. Although the consultant psychiatrists advised the patients included in studies 1 and 3 that alcohol use should be kept to a minimum due to its incompatibility with hormone treatment, it is difficult to know whether patients choose to follow such advice. One might hypothesise it to be a confounding influence in the present research, particularly as transsexuals may turn to alcohol as a means of coping with their gender dysphoria. However, it is not known whether alcohol abuse would be a systematic influence in studies from studies 1 and 3. Again, further research would be informative in how influential alcohol is on memory, cognition and mood, as would obtaining data on alcohol use in research participants.

5.2.5. Sex of Researcher and experimenter/participant biases.

Previous research has reviewed male and female researchers across studies and found that female researchers were significantly more likely to detect sex differences favouring females in verbal abilities, than male researchers (Hyde and Linn, 1988). In the present thesis, sex of researcher (female) was consistent across situations for both studies with transsexual populations. Further, the present researcher was not blind to the directional hypotheses in studies 2 and 3 and was aware of the hormonal status of the transsexual participants. It is possible, as with other research in this area, that unconsciously the researcher may have altered performance of the participant leading to demand characteristics. However, it is unlikely in the present study as those taking hormones in the third study (Chapter 4) did not perform better than those not taking hormones on tasks at which females excel or perform worse on tasks at which males excel. In other words, these data did not conform to the experimenter's expectations. It is an important consideration however for future studies to report the sex of researcher in order to assess the influence of this variable. For example, it would have been of interest in the present thesis to be able to include sex of researcher as a factor that might have influenced magnitude of sex differences in memory tasks selected in study 2 (Chapter 3).

5.2.6. Situational variables

As mentioned previously in Chapter 1 it is of fundamental importance to ensure that all research participants experience the same, or similar, situational settings. The participants from studies 1 and 3 were administered the same tests, in a counterbalanced order, using standardised instructions, in a hospital environment. However, the studies reviewed in study 2 were tested in a variety of situations and this might have contributed to variability in findings.

Another factor discussed earlier involves the treatment of the participants in studies 1 and 3. They were administered differing dosages of various hormones for varying durations of time. This is discussed in Chapter 4 discussion and summarised in Table 33. Hormone type and administration could not be controlled here and this may have contributed to differences between study 1 (Chapter 2) and study 3 (Chapter 4). It might also contribute to large variability among other studies looking at oestrogenic effects on memory, mood and cognition.

5.2.7. Publication bias

Of final consideration is that the world of research is exposed to bias information. Researchers do not have access to information about all the studies that find no influence of sex hormones on cognition or sex differences in cognition. This involves the tendency for peer reviewers to accept positive findings for dissemination while the negative findings are left in the 'file drawer' (Rosenthal, 1979). It is possible that all oestrogenic effects or sex difference in cognition are spurious and there is a larger proportion showing null findings. All researchers in this and other areas of research must be open-minded in interpreting research findings.

5.3. Theoretical Implications of these data: Memory and cognition

Largely the present data do not provide support that oestrogen influences memory or cognitive abilities in M-F transsexuals. This may be due to methodological limitations discussed in the previous section, which might render the negative findings of no importance. Alternatively, the present findings may suggest limitation on the conclusion that oestrogen influences abilities. This section will discuss the present findings in context of the following theoretical perspectives reviewed in the introduction: i) Hormonal influence on sexually-dimorphic tasks; ii) The androgen/oestrogen balance model; iii) Organisational versus activational influences of hormones on memory and cognition; iv) Brain lateralisation theory; v) The effects of mood on memory and cognition; vi) The effects of hormones on mood vii) Age and memory/cognition.

5.3.1. Hormonal influence on sexually-dimorphic tasks

Overall the present data for M-F transsexuals do not provide support for the hypothesis that oestrogen enhances memory or cognitive abilities at which females excel and impairs memory or cognitive abilities at which males excel. Firstly, in study 1, oestrogen did enhance performance on the Verbal PAL task, at which females excel, yet no other sexually-dimorphic

cognitive task was influenced. Secondly, the enhancement in Verbal PAL was not replicated in study three, suggesting findings from study 1 were spurious. Findings from study 3 are more reliable and powerful than findings from study 1, due to its repeated measures design, eliminating possible confounding factors not considered in the first study e.g., sexual orientation.

Some findings from study 3 could be interpreted to suggest that oestrogen influences sexually-dimorphic tasks, although the findings may be unreliable, given that so few of the many abilities assessed were altered and that results were not parallel for those off then on and those on then off oestrogen. Performance on Visual PAL, a task hypothesised to favour males, improved when hormones were withdrawn, whereas performance on Object memory, a task that favours females was impaired when hormones were withdrawn. However, DS, a control task showing no sex difference, also differed for those on and off hormones, suggesting that effects were not specific to sex dimorphic tasks. Further, no oestrogenic influence on other tasks that show larger sex differences, such as Mental Rotations, was found in either study 1 or study 3. Therefore, oestrogenic influence on cognition may not be limited to sexually-dimorphic tasks, or may not be found at all.

Also, findings from study 2 examining sex differences in memory suggest that Object memory does not show a reliable sex difference and further research is needed to examine how stable these sex differences are before we can conclude that oestrogen influences memory and cognitive tasks that show sex differences. Nevertheless, overall, the findings provide little or no support for the hypothesis that oestrogen specifically enhances performance on tasks at which females excel or impairs performance on tasks at which males excel.

5.3.2. The androgen/oestrogen balance model (Nyborg, 1984; 1988; 1990).

This theory proposes that, with general intelligence controlled, there is an inverse relationship between spatial and verbal abilities. Further, it suggests that oestradiol is the critical hormone in the expression of spatial abilities. The main principle behind the theory proposes that there is a dose-dependent effect of oestradiol on spatial abilities. Either too much or too little of the hormone is damaging to spatial abilities, while intermediate levels of oestradiol are thought to optimise spatial abilities. Activational

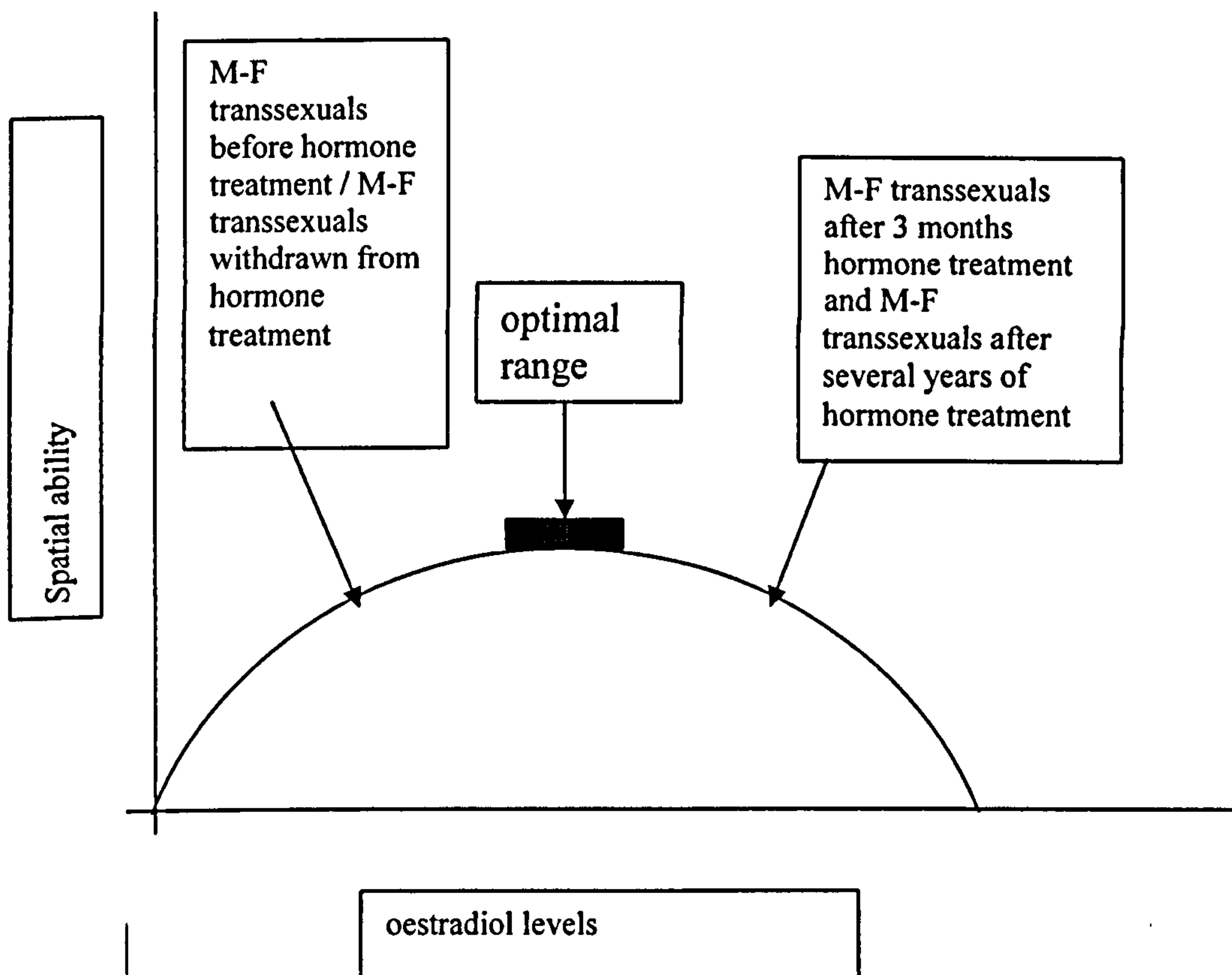
effects of short-term changes in oestradiol levels on memory and cognition are also predicted with this theory.

Relating this theory to the present findings for M-F transsexuals, short-term treatment, long-term treatment or withdrawal from hormone treatment did not produce change in spatial performance of M-F transsexuals in studies 1 and 3. Therefore, at least on the surface it would seem that the present findings do not support this dose-dependent effect of oestradiol on spatial ability. Given the predictions of optimal oestrogen range, it is unlikely that linear relationships will occur between cognitive performance and dosage of treatment. Our findings suggest that no significant linear relationships between memory or cognition and dosage of treatment exist. However, as the present study did not measure actual hormone levels, it is not possible to completely rule out the possibility that curvilinear relationships exist between hormone levels and spatial performance.

Conversely, there are ways to reconcile Nyborg's theory with the present outcomes in M-F transsexuals, but only by making certain assumptions that may or may not be true. A possible explanation of the lack of oestrogen effects on memory and cognition in M-F transsexuals from studies 1 and 3 may be that oestrogen treatment may exceed the optimal range. Therefore,

no change is observed in performance as a result of oestrogen treatment. See Figure 13 for these hypothesised effects of oestrogen on spatial ability in the present groups of M-F transsexuals. However, as hormone levels were not measured in studies 1 and 3, we cannot test this hypothesis.

Figure 13: Hypothesised effect of oestrogen treatment on spatial ability in M-F transsexuals throughout their treatment



The theory further explains individual differences in spatial performance within sexes. Individual variation in spatial performance may be due to

factors such as early steroid priming, age-related changes in target tissue responsiveness, oestradiol production rate and metabolic clearance. These factors may all be expected to relate to the optimal oestradiol range (Nyborg, 1983). Past research has found that a relative abundance of oestradiol favours physically feminine features, while a relative abundance of testosterone favours physically masculine features (Marshall and Tanner, 1970). There is the assumption that, in androgynous men, there are slightly increased oestradiol levels, which would bring them within the optimal oestradiol range for the enhancement of spatial ability (Nyborg, 1983). Further studies on relations between sex hormone levels, bodily features and spatial ability in men are needed to test this theory. With this population of M-F transsexuals, a particular dosage of oestrogen differentially affects secondary sex characteristic development. Hormone dosage varied because each patient's physician prescribed hormones in the light of each patient's presenting clinical picture and history, as well as their physical response to hormone treatment. Therefore, higher dosages may be required to achieve physical feminisation in one M-F transsexual than is required in another M-F transsexual. Also, those commencing treatment may be given small dosages to relieve their dysphoric mood, yet not to achieve physical feminisation at that particular stage of their treatment. If physical and cognitive feminisation correlate, then some of the

transsexuals in study 3 may not be physically feminised, and so will not cognitively feminised, as a result of short-term treatment, with low dosages of oestrogen. Whilst physical feminisation may be a factor in explaining our overall negative findings, the assumption that physical femininity is related to cognitive femininity needs to be tested. If the extent of physical feminisation relates to spatial ability, then the degree to which the hormone treatment physically changes the transsexuals may be an important consideration in future research that looks at effects of cross-sex hormones on memory and cognitive performance.

This theory may also be useful in considering within-sex differences in spatial ability to be based on biochemical individuality. The emphasis on individuality also has consequences for the traditional view on sex differences in spatial ability, explaining considerable overlap between the sexes. It might also contribute to the variability in sex differences found in the second study examining sex differences in particular memory tasks.

In summary, the present data for M-F transsexuals and sex differences in memory appear to argue against Nyborg's theory. Whilst arguments have been proposed to explain the present overall findings for M-F transsexuals

through individual differences in physical femininity or physical masculinity, there are no data yet to support these assumptions.

5.3.3. Organisational versus activational influences of hormones on memory and cognition.

The present findings for M-F transsexuals do not parallel findings suggesting oestrogenic influences on memory and cognition in women. Activational effects of oestrogen treatment on memory and cognitive tasks in M-F transsexuals were not reliably seen. It is therefore possible that men and women may be differentially influenced by the activational effects of oestrogen. This point can be illustrated by referring back to the study examining Verbal Fluency in both M-F and F-M transsexuals before cross-sex hormone administration and three months after hormone manipulation (Van Goozen et al, 1995). A small, non-significant decrease in Verbal Fluency in M-F transsexuals was found following oestrogen and anti-androgen treatment, yet a significant decrease in verbal fluency in F-M transsexuals was found following androgen administration.

The androgen administration may have interfered with normal ovarian functioning, decreasing the amount of circulating oestradiol in F-M transsexuals. As the F-M transsexuals were more adversely affected by the

decrease in oestradiol than the M-F transsexuals were helped by the increase in oestrogen in this study, the results indicate that oestradiol may enhance women's Verbal Fluency production, more so than men. Further research would include F-M transsexual populations to determine whether cross-sex hormone treatment influences females, more so than in males, in a variety of verbal and spatial tasks. It would also be helpful to include hormone measurements to determine whether it was oestrogen or androgen that may be responsible for the observed changes in cognitive performance.

Recent research has found sex differences in episodic memory involving words, stories and faces (Yonker, Eriksson, Nilsson and Herlitz, 2003). The sample consisted of older men and women matched on circulating levels of oestradiol, therefore oestradiol level must not be the only contributing factor to sex differences in performance. It is suggested that the early prenatal influence of oestrogen on the developing brain makes the brain organisation more receptive to the influence of oestradiol in an adult woman's life than in the adult male's life (Maclusky, Bowlby, Brown, Peterson and Hochberg, 1997).

It could be suggested that in men, organisational effects of oestradiol may be more important influences on memory and cognitive performance than

activational influences of oestradiol, since the direct manipulation of active oestradiol did not change the sex-typical behaviors that may have arisen from the organisational influence of oestrogen in development. However, the present research did not measure organisational influences of oestrogen on memory or cognitive performance, so we cannot conclude that organisational influences of oestrogen on human cognitive performance are more important. Indeed, other studies suggest that oestrogen has little or no organisational influences on human cognitive performance (Hines and Shipley, 1984; Hines and Sandberg, 1996). Further, negative findings of activational influences of cross-sex hormones have been explained by the suggestion that homosexual transsexuals do not respond to activating influences of oestrogen (Van Goozen et al, 2002). Further research is needed to verify these suggestions. On the other hand, whether there are sex-typical behaviours that occur early in development or later after puberty in memory remains questionable as sex differences in particular memory tasks were not reliably seen in study 2 (Chapter 3).

5.3.4. Brain lateralisation theory (Geschwind, 1983; 1984; Geschwind and Galaburda, 1987).

In relating the present findings for M-F transsexuals to brain lateralisation theory, it is important first to outline the assumptions of this theory. There is evidence to suggest that males and females differ with respect to hemispheric cerebral organization (McGlone, 1980). There are sex differences in hemispheric lateralisation and, it is suggested that these sex differences are influenced by prenatal hormonal factors. These sex differences are thought to underlie the sex differences in cognitive functioning (Geschwind, 1983; 1984; Geschwind and Galaburda, 1987). More specifically, females, like left-handed individuals are more likely to be bilateral for verbal function, which, in turn, inhibits the development of spatial processing capabilities, which the theory asserts will develop best with great lateralisation of function. Male superiority in spatial ability and female superiority in verbal ability is suggested to be due to these differential patterns of lateralisation.

The present research with M-F transsexuals did not measure lateralisation. We measured cognitive functions, some of which are assumed to be more localised to the left or right hemisphere. Information about sex differences

in the way the hemispheres are specialised comes from brain lesion studies outlined in the introduction. Left hemisphere damage reduces verbal test scores, whereas right hemisphere damage leads to a reduction in non-verbal abilities (see Mountcastle, 1962; Gazzaniga, Ivry and Mangun, 1998 for review). The battery of tests given to the M-F transsexuals was assumed to consist of tasks localised to the right or left hemisphere on the basis of their verbal/non-verbal nature.

In studies 1 and 3, there is little consistent evidence to suggest that activational effects of oestrogen influenced tasks assumed to rely on either left or right hemispheric processing. Hormone treatment did not produce a change in performance in right-hemisphere dependent tasks (MR and JOLO) or left-hemisphere dependent tasks (verbal memory and Verbal Fluency). Furthermore meta-analytic findings from study 2 suggest that there may be was no consistent evidence of sex differences in memory tasks localised to either the right or left hemisphere.

It has been hypothesised that high levels of oestrogen may facilitate left hemispheric processing relative to right hemispheric processing, therefore hormones can have activational effects on cerebral asymmetry as well as perinatal organisational effects (Kimura and Hampson, 1993). Abnormal

perinatal hormonal environments have been shown to influence the development of patterns of perceptual asymmetry. For example, prenatal DES exposure to females was associated with a more masculine pattern of lateralisation (i.e., a stronger right-ear advantage) than their sisters on a verbal dichotic listening tasks, although there were no differences between these groups in verbal and spatial ability (Hines and Shipley, 1984). However, no activational effects of oestrogen on perceptual asymmetry were found using verbal and non-verbal laterality tasks, in women during the menstrual cycle (Compton and Levine, 1997).

The question as to whether activational or organisational effects of hormones influence brain lateralisation patterns remains unresolved from the present research with M-F transsexuals. Future research might examine whether brain asymmetry patterns change as a result of hormone treatment, by using tasks more sensitive to brain asymmetry, such as dichotic listening. However, what can be concluded is that if cross-sex hormone treatment did have activational effects on brain asymmetry patterns, the present research with M-F transsexuals did not support the assumption of a reliable change in cognition as a result.

As with all these theories discussed in this section, it could be hypothesised that the effects of oestrogen treatment on cognitive abilities in men do not parallel the effects observed on cognitive ability when oestrogen treatment is given to postmenopausal women.

5.4. Theoretical implications of the data: Mood

In relating the findings of mood from the present research in a theoretical context, two areas will be addressed: i) The effects of mood on memory and cognition; ii) The effects of hormones on mood.

5.4.1. The effects of mood on memory and cognition

The two moods, composure and confidence, correlated positively with performance on a variety of memory and cognitive measures in the third study (Chapter 4), irrespective of their verbal or visual-spatial nature. These data provide support for the resource allocation model that has been used to describe the disruptive effects of mood on memory and cognitive performance (Ellis and Ashbrook, 1988). The theory proposes that all tasks require some allocation of capacity to process the information and that distressing mood reduces this capacity to process the task. Therefore, the

present findings support the resource allocation model that negative moods, such as anxiety and feeling unsure is positively related to poorer performance, presumably as these feelings put a strain on processing capacity. Given these findings, mood effects may contribute to variability in the sex differences summarised in study 2.

5.4.2. The effects of hormones on mood

It is difficult to draw conclusions as to whether the mood enhancements seen in these transsexuals commencing treatment can be attributed to direct, activational hormone effects or, as mentioned previously (Chapter 4), whether they occur as expectancy effects that patients have as a result of starting hormone treatment. No change in mood was observed in those transsexuals withdrawing from hormone treatment, therefore, one might presume that the mood enhancements were not a hormonal effect. However, the five-week period of hormone withdrawal may not have been sufficiently long to deplete the long-term hormone treatment undergone by these transsexuals. Biological explanations propose that oestrogen increases serotonin, which subsequently increases MAO levels. A widely accepted hypothesis is that depression is associated with a deficiency of serotonin in the brain. However, we cannot infer that MAO levels have

increased as a result of oestrogen treatment in these transsexuals, with a subsequent effect on mood, because we did not measure MAO levels. Until future research establishes a relationship between measured MAO levels in similar populations undergoing hormone treatment, the actual cause of the observed mood enhancements found in the third study, remains unclear.

5.4.3. Age and memory/cognition

As outlined in the introduction, changes in neurotransmitter and neuroendocrine functions later on in life could be responsible for some of the decline observed in memory and cognitive function. For study 3 we explored possible relationships between age and performance. As expected vocabulary, used as a measure of general intelligence, correlated positively with the majority of outcome measures. A negative association between Visual PAL and age was seen, however, which supports previous findings of associations between age and secondary memory processes (Gilbert and Levee, 1971).

Complex associations of age with LM and VR were detected in the meta-analysis. These associations were positive in direction, suggesting that as

age increases so too does performance on these measures, however further inspection of these graphical relationships suggested otherwise. The sex difference in LM favoured males in early years and then gradually reversed over subsequent years favoured females. Oestrogen levels and testosterone levels decrease with age. Findings could be explained by testosterone levels declining, as this task is thought to favour females, however, it is not known whether the older women from these studies were taking oestrogen replacement therapy, in which case, activational influences of oestrogen on this task may be plausible. Further research to support these age associations with memory performance is needed.

The gradual reduction of sex differences in VR favouring males shown in study 2 is also a finding in need of replication. Findings may be attributed to lowering oestrogen and testosterone levels, assuming no HRT is given to these elderly women. Without hormone profiles of participants however, these hypotheses are merely tentative.

5.5. Final comments

The present thesis has contributed to our understanding of the influences of activating gonadal hormones on memory, cognition and mood. It may also

have added to previous confusion and conflicting results from past data advocating oestrogen and other gonadal hormones as a therapy for women and men. Of main concern to researchers in this area is the lack of control for possible confounding factors such as mood, the different measures used among studies, alcohol consumption, nicotine intake, time of day or year and other methodological factors mentioned in this concluding chapter. It is unclear from the studies presented in this thesis whether the groups of transsexual patients differed systematically in these respects. Until these are considered in future research and more importantly, until consistent findings are demonstrated, it is premature to conclude that oestrogen or other gonadal hormones can be used as a tonic for the mind, as an effective therapy for depression or as a use for the prevention or onset of AD.

In the search for factors that influence achievement levels, single explanations cannot adequately account for the observed sex differences.

Sue and Okazaki (1990), p. 913.

APPENDIX

Appendix 1: Hormones and Behavior (1998) publication (Chapter 2)

**PAGE/PAGES
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UNDER
INSTRUCTION
FROM
UNIVERSITY**

Appendix 2: Consent form (Chapter 4)

Consent form

I _____ agree to participate in a study of the effects of sex differences on tasks known as ‘Cognitive skill’, which involve paper and pencil measures of verbal and visual-spatial abilities, memory and questionnaires assessing my mood. Testing does not involve any risk to me. These procedures take approximately one and a half hours.

The procedures will be given once and I will be paid £10. for my participation. I understand that I do not have to agree to participate in this study. I may withdraw from the study at any time. If I do withdraw or do not participate, I will not receive payment.

Date.....

Signature.....

Name Printed.....Witness.....

Appendix 3: Handedness Questionnaire (Chapter 4)

Handedness

The next 5 questions ask about your hand preferences for writing and other tasks.

For each task please circle the number that most closely describes the hand you prefer to use.

		<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>
		<u>Right</u> <u>always</u>	<u>Right</u> <u>Usually</u>	<u>Right</u> <u>and Left</u> <u>usually</u>	<u>Left</u> <u>Usually</u>	<u>Left</u> <u>always</u>
<u>A</u>	<u>Writing</u>					
<u>B</u>	<u>Throwing a ball</u>					
<u>C</u>	<u>Holding a pair of</u> <u>scissors to cut</u>					
<u>D</u>	<u>Holding your</u> <u>toothbrush</u>					
<u>E</u>	<u>Drawing</u>					

Appendix 4: Patient Information Sheet

Patient Information Sheet

ID no.-----

Date-----

1. What is your date of birth?-----
2. Hormone Status:
 - Are you currently taking hormones?-----
 - Name of hormone?-----
 - Dosage of hormone?-----
 - How long have you been taking hormones?-----
 - Previously have you ever taken hormones?-----
 - If so, when, which hormone and what dosage?-----

3. What is your occupation?-----
4. How far did you go in school?-----
5. Once having started hormone treatment, do you or did you expect to think, feel or perform differently?-----
6. Are you taking other medications?-----
--
7. Do you have any medical problems?-----
--
8. Patient Charing X ref. No.-----

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