The relationship between gonadal hormones and neurocognitive functioning in healthy men and women and patients with schizophrenia

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Rozmin Halari

City University

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Acknowledgements

This PhD thesis is a dedicated focused effort in trying to understand the relationship between gonadal hormones and neurocognitive functioning. I am grateful to Dr Veena Kumari and Professor Melissa Hines for their valuable guidance throughout these years, contributing clarity and focus during their supervision.

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Summary

The primary aim of this thesis was to examine differences between healthy men and women and men and women with schizophrenia in relation to neurocognitive functioning. The thesis also examined the role of organisational influences of gonadal hormones and gonadotropins to cognitive performance. This was investigated in three studies. Study 1 examined the differences between healthy men and women on a sexually dimorphic cognitive battery (comprising mental rotation, modified judgement of line orientation, computerized Benton judgement of line orientation, cognitive inhibition, letter and category fluency tasks, and a working memory task) in a group of healthy men (n= 42) and women (n = 42). The study also looked at the relationship of organisational influences of gonadal hormones (estrogen, testosterone, progesterone), gonadotropins (lutenizing hormone; LH, follicle stimulating hormones; FSH) and sex hormone binding globulin; SHBG to these cognitive tasks. Study 2 investigated the role of gonadal hormones and the stress hormone cortisol to neurocognitive functioning (comprising domains of attention, verbal abilities, language, memory, executive functioning, motor and speed of information processing) and symptomatology (using the Positive and Negative Syndrome Scale; PANSS) in patients (N = 37) with schizophrenia. Study 3 examined the neural correlates of sex differences in performance on a block design mental rotation task and an overt verbal fluency paradigm using compressed sequence design in a group of healthy men (n = 9) and women (n = 10), controlling for the role of estrogen. Study 1 showed significant sex differences favouring men on all the spatial tasks and on a cognitive inhibition task, and differences favouring women on the category fluency task. Significant relationships were found between specific conditions of the spatial and inhibition tasks and progesterone, LH, FSH and SHBG. Study 2 found no sex differences in neurocognitive performance in patients with schizophrenia but found that high levels of estrogen were related to low positive symptom scores. Within gender, cortisol levels related to poor performance on the information-processing domain. Study 3 showed sex differences favouring men on the mental rotation and

favouring women on the verbal (phonological) fluency task. Analysing the sexes separately revealed activation in the right superior parietal lobe in men and women during mental rotation performance. In general, women activated a greater number of voxels compared to men on the mental rotation and verbal fluency tasks. No sex differences (comparing the groups) in neural activation were found on any of the cognitive tasks. These findings confirmed the previously cited sex differences in cognitive performance and show that with similar activation patterns, men and women showed differential behavioural performance, thus suggesting that women may need more resources to perform better. Overall, this thesis adds to a critical body of literature showing that the relationship between gonadal hormones and cognition is more unsettled than previously thought. The findings also show that hormones other than estrogen and testosterone may also moderate hormone cognition relationships in men and women.

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Chapter 1: SEX AND NEUROCOGNITION

1.1 Introduction

From the beginnings of experimental psychology, sex differences in neurocognitive performance have been explored with fascination. The majority of studies agree that (on average), men will outperform women on tests which depend on transformations in visuo-spatial working memory (e.g. mental rotation), and on mechanical and mathematical reasoning tests (Maccoby and Jacklin 1974; Halpern, 1992, 1997; Voyer et al., 1995). Women, however, are reported to excel at tasks of verbal fluency (rapid and accurate generation of words and verbal meanings), and also on tests of fine motor skills such as the Purdue Pegboard task (Halpern, 1992,1997; Collaer and Hines, 1995; Kimura, 1999). They also outperform men on tests of verbal memory (Paired Associate Learning and Story Recall (Des Rosiers and Ivison, 1988; Ivison, 1977; Mann et al., 1990), performance of fine motor-coordination tasks, object memory location tasks, and navigation which uses landmarks as points of reference (Halpern, 1992; Kimura; 1999; Silverman and Eals, 1992). Men on the other hand, tend to outperform women on gross motor tasks, and navigational ability, which uses distance orientation and accurate targeting. Men also are expected to perform better on tasks requiring cognitive inhibition, which is the ability to select the most relevant of stimuli, to the exclusion of the irrelevant (Broverman et al, 1968). However, no sex difference has been reported in performance of tests of verbal memory, such as digit span (Blum et al., 1972; Chavez et al., 1983; Makarec and Persinger, 1993, 1995).

The aforementioned behavioural studies generally use measures of performance (accuracy) and reaction times, with effect sizes (defined as the mean standardised difference between the scores of men and women on a specific test) ranging from about 0.3 to 0.9 (the largest effect sizes are for mental rotation; Linn and Petersen, 1985; Collaer and Hines, 1995). However, Feingold (1988) and Hyde and Linn (1988) have questioned the very existence of sex differences in cognition, arguing that these differences may be disappearing or are not as strong as were previously thought. This

doubt also extends to the area of sex differences in functional cerebral asymmetry; there is often a tendency to attribute the sex differences found in cognitive domains to differences in cerebral lateralisation. Usually, it is claimed that the male brain is more lateralised than the female brain (McGlone, 1980), though some recent studies have suggested that lateralization of the male brain refers to verbal functions alone, and that bilateral processing is evident in spatial functions (Gur et al., 2000).

Of course, the true nature of cognitive sex difference must still be explored, as it is by no means fully understood. Maccoby and Jacklin in 1974 coined a term for one of the problems with understanding sex differences, the "file drawer problem", meaning that those studies which often remain unpublished in this area of research are those which do not yield significant findings. This is a valid consideration but there is good evidence supporting the existence of at least some cognitive sex differences. For instance, a meta-analysis by Voyer et al. (1995) showed that, in tests of sex differences in spatial ability, men excelled on these tests to the extent that over 178,000 studies with null findings would be needed to offset those results, which were significant. Hyde and Lynn (1981), in their meta-analysis of verbal abilities (including vocabulary, verbal fluency, verbal analogical reading, and reading comprehension), found a 79:21 ratio of findings, which showed women excelling in this area. Hiscock (1995) found that of 219 lateralisation studies, only 31% showed significant sex differences, but 17 supported greater lateralisation in men, of 20 that satisfied stringent criteria for inclusion. Hahn, in his 1987 review, showed an 83.17 ratio of findings for greater male cerebral lateralisation. These findings, taken on the whole, show a strong case for sex differences in neurocognitive functioning.

It is accepted that, within this field of research, there are many studies, which fail to achieve a significant finding, but this can perhaps be explained by examining the terms used within the research. “Spatial abilities” and “verbal abilities” are very loose semantic terms, nonetheless used very often by researchers. By separating spatial and verbal functions, and by focusing on domain-specific cognitive neurofunctions (Kolb and Whishaw, 1995; Lezak, 1994), a different pattern of sex difference can be examined; one

which acknowledges the existence of task-specific sex differences, and within sex differences (Voyer et al., 1995; Sanders et al, 2000).

To summarise, neurocognitive functions at which men are reported to excel include: mental rotation, spatial perception, finding simple figures embedded in complex patterns ("disembedding"), navigation which does not rely on landmarks, gross motor co-ordination, and mathematical reasoning with problem solving. Women, on the other hand, seem to excel on tests of both phonological and category fluency, perceptual speed and accuracy, fine motor co-ordination, and spatial location memory for objects. (See Halpern, 1992; Kimura, 1999; Voyer et al., 1995). Some women will always be found to perform better on what are perceived as "male" oriented tasks, and vice versa, males performing in "female" directions (Hyde and Linn, 1988). This overlap in the distribution curve in perceived areas of sex differences could have many explanations. The current thesis focuses on the possibilities that explain part of this within sex variation.

This section will aim to examine and explore sex differences in the different cognitive domains and the subsequent sections will discuss the various influences on these sex differences and also, where relevant, the variations within those differences.

1.2 Sex Differences in Cognitive Functions

1.2.1 General Intellectual Abilities

Despite the cognitive differences reported between the genders, most researchers suggest no sex difference in general intellectual ability (that is, "general intelligence" or "g", e.g. Collaer and Hines, 1995; Geary, 1998; Halpern, 1992; Jensen, 1998; MacIntosh, 1996). The effect sizes that are found for general intellectual ability (< 0.10) are generally considered negligible. For example, the WAIS scale (Weschler Adult Intelligence Scale), a popular and widely used intelligence test, was designed to omit sex-biased factors. Most tests of intelligence however would not have items that would show sex differences. Such items if found would be removed during the development of tests. Nevertheless, according to Lynn (1994), there is a slight advantage to the male. Older studies, which used the WAIS, do not support this finding; however, most researchers

have found that any sex differences in this test are component-specific (e.g., men outperforming women on the information sub-tests, and women outperforming men on digit-symbol sub-tests (Snow and Weinstock, 1990).

In another relevant study, Colom and Garcia-Lopez (2002) tested 1772 women and 2300 men who were high school graduates, and found that the PMA (Primary Mental Abilities) inductive reasoning sub-test favoured women, while the APM (Advanced version of the Raven's Progressive Matrices) favoured men. The authors of this study, however, point out that the female superiority of performance could be due to the verbal content of this test, whilst the males could perhaps have shown better performance on the APM because it was based on figures (there were no sex differences found in Cottrell's Culture Fair Test). The overall effect size of the sex difference was small, in fact just 0.19 for the PMA and 0.28 for APM, but from this the authors concluded that Lynn's argument (1994) for male superiority in fluid intelligence of Gf (a definition of intelligence (G), measured by the Raven's Progressive Matrices test; SPM), lacks solidity; the authors argued that the cognitive sub-tests must be considered, usually under those broad terms "spatial abilities" or "verbal abilities".

Gf measured by the Raven's Progressive Matrices test (SPM), was proposed by Mackintosh in her 1996 study on a sample of Israeli military conscripts. The author found no sex differences in SPM scores on her data. The test used in this study, however, was only one version of the actual SPM; furthermore, the female sub-sample in this study was not fully representative. This therefore does not demonstrate a valid way to measure sex differences on the SPM. In one review by Hedges and Nowell (1995), 6 US national probability studies (over a 32-year time period) were subjected to the analysis of academic achievement scores. The findings showed that men showed a larger variance in scores on most tests, and also that there were more men found in the higher range (or upper tails) of the scores distribution. However, tests of reading comprehension, perceptual speed and associative memory were the exceptions to this rule, and these tests found men to perform at the *bottom* end of the scoring distribution. Pind et al. (in press) conducted a study on 66 children between 6-16 years of age, and found no evidence for

sex differences in the Raven's SPM scores. Further evidence to support this conclusion comes from a review by Court (1983) of 118 studies, which yielded ambiguously mixed results. Higher mean scores from the women, higher scores from the men and no sex difference at all, were all variously reported from different studies in the review. The authors of this review concluded that there was no demonstrable evidence for a sex difference for the Raven's SPM. There is however evidence from one study ((Kumari and Corr, 1996) of menstrual cycle effects during performance on intelligence tests. In this study, subjects were tested under high and low arousal- induction conditions (with vs without time pressure instructions) during either the midcycle or menses phase of the menstrual cycle on SPM and Hundal's general mental ability scores. The results showed a crossover interactive effect of menstrual phase and stressed-induced arousal on performance of the Hundal's test, suggesting that performance of subjects who were tested during the midcycle phase (high basal arousal) was impaired under the time pressure instructions condition (high induced arousal) as compared to performance under the without time-pressure instructions condition (low induced arousal), with the reverse pattern of findings shown for subjects who were tested during the menstruation phase. There were no menstrual effects found for performance on the Raven's SPM.

The answers to the questions of whether sex differences in general intelligence exist, and whether they would be test-specific if they do, are frustratingly unclear. The difference between the sexes in general intelligence is still a fiercely contended area of research. Sex differences in general intelligence have been extensively studied and the general conclusion that most investigators have reached is that some tests show a slight female advantage and some a slight male advantage, but these are < .10 standard deviations and so viewed as negligible. An additional relevant point is that one could make intelligence tests that favour either men or women if one desired, so that an attempt can be made to eliminate any disagreement of sex-bias this area of research.

1.2.2 Spatial Cognition

Many authorities have reported sex differences in certain cognitive functions. The sections that follow will discuss these functions in turn. The first cognitive ability to be

discussed here is the domain in which the largest difference, in effect size, between men and women, can be found: that of "visuo-spatial functions". Visuo-spatial functions are measured using tests that require rotations, manipulations or transformations of visually presented patterns. These tests are classified into several groups with different demands on processing: mental rotations of 2 or 3-dimensional forms, spatial orientation, spatial perceptions (determining the vertical or horizontal planes), maze navigation, and disembedding tasks or spatial visualisation (Borich and Bauman, 1972; Ekstrom et al., 1976; Michael et al., 1951; Astur et al., 1998; Kimura, 1999; Linn and Petersen, 1985; Moffat et al., 1998; Voyer et al., 1995). All of these processing abilities are usually grouped under the broad term "spatial (or visuo-spatial) abilities " (Moffat and Hampson, 1995). In all cases men excel at these tasks to a greater extent compared with women.

Maccoby and Jacklin, in their book of 1974, attempted to summarize the existing literature on sex differences. They reached conclusions that verbal and spatial abilities (along with behaviours such as aggression and childhood play) show sex differences. However, their meta-analysis was not widely understood or used at the time, and they could not say how large these sex differences were, or even if they were significant. Subsequent, meta-analysis allowed researchers to determine how large the sex differences were, and the accrual of additional studies allows one to look at different subtypes of spatial ability and verbal ability. As a result, this led to meta-analytic evidence that provides fairly accurate estimates of the size of sex differences in various sub-types of spatial and verbal abilities, and, in some cases, of the size of sex differences on specific tests. Statistics used in these meta-analyses have also allowed us to determine that these sex differences are large enough to override any possible "file drawer problem" at least for certain sub-abilities.

Hyde, in 1981, meta-analysed the results of the review on sex differences by Maccoby and Jacklin (1974), and found that sex differences accounted for just 5% of the variance in the sampled tasks. The suggestion to be taken from Hyde's meta-analysis is that gender has very little influence on spatial test scores (see Caplan et al., 1985; their conclusion is that in this area, the sex differences are too slight and too variable to draw

any definite conclusions). Caplan et al. (1985) point out that, as many researchers and their studies do not actually provide a clear definition of spatial ability, it is difficult to compare the results of varied studies, as it is impossible to know precisely what aspect of spatial ability is being measured in each study.

From this perspective, Caplan et al. (1985) disputed the findings of an earlier meta-analysis by Linn and Peterson (1985), which found sex differences in spatial perception to be clear and evident. Linn and Peterson (1985) conducted a meta-analysis, in which they collected data from the studies carried out *since* Maccoby and Jacklin's 1974 review. The authors, using a psychometric rationale in addition to the cognitive, classified the spatial tests into categories, achieving effect sizes based on Cohen's *d* (1988), which were as close as possible to homogenous. They found 3 groups of spatial categories: (1) Spatial Perception (mean effect size: 0.44), (2) Mental Rotation (mean effect size 0.73), and, (3) Spatial Visualisation (mean effect size: 0.13).
From these findings, it is evident that this review found a strong case for sex differences, somewhat undermined by Caplan et al's previously mentioned criticisms.

The criticisms outlined by Caplan et al. (1985), were considered in a meta-analysis conducted more recently by Voyer et al. (1995), in which data were collected on sex differences in a variety of specific tasks designed to measure spatial ability. Two hundred and eighty six effect sizes were analysed, and the conclusions of this study were that male performance was superior to a significant level on the paper form board, the PMA (Primary Mental Abilities) spatial relations test, cards rotation test and generic mental rotation tasks. Incidentally, most researchers agree that mental rotation is the largest male-favouring task, although a large difference also appears to be on maze navigation (as will be discussed later).

Recent studies show that for mental rotation the effect size ranges from 0.50 to 1.00, for spatial perception from 0.40 to 0.74, for spatial visualisation from 0.50 to 0.74, and for maze navigation from 0.54 to 1.59 (Astur et al., 1998; Moffat et al., 1998; Voyer et al., 1995). These figures, and the large sex differences here, may be due to the powerful

association between the tests of maze navigation (e.g. Virtual Morris Maze) and mental rotation (which will be more fully discussed later in this chapter).

Voyer et al. (1995) found that, of all the tests analysed, the strongest sex difference was found on the mental rotation test. The notion that the magnitude of sex differences is decreasing over recent years found some partial support in this analysis, but it is important to note that these differences were still found to be significant over a number of tests; they can be by no means said to have disappeared. Voyer et al. (1995) attempted to explain the possible decrease in sex differences with the fact that attitudes towards cognitive differences have changed, and so this attitude change has affected the way that men and women approach certain tasks. It is possible that these changes of attitude affect the way in which children of both genders are brought up. The authors also concluded that the age of emergence of sex differences depends on which test is being used.

1.2.2.1 Mental Rotation

Mental rotation tasks are thus of great interest to the sex difference researcher, because there is reliable evidence that three-dimensional mental rotation tasks show a large sex difference. The mental rotation tasks involve "imaginal rotation" (the subject imagines what the stimulus figure or object might look like when viewed from different orientations in space). The subjects are instructed to decide whether the two shapes are the 'same' or 'different'. Shepard and Metzler (1971) were the first to produce a mental rotation task based on 3-dimensional cuboid figures, but the test, which is usually used now, is a modified version developed by Vandenberg and Kuse (1978). The varying orientations of the 3-dimensional figures in this test are parallel to the picture plane (or slightly tilted to it), and thus the core processing involved in this test is assumed to be "rotational" (See Figure 1 below).

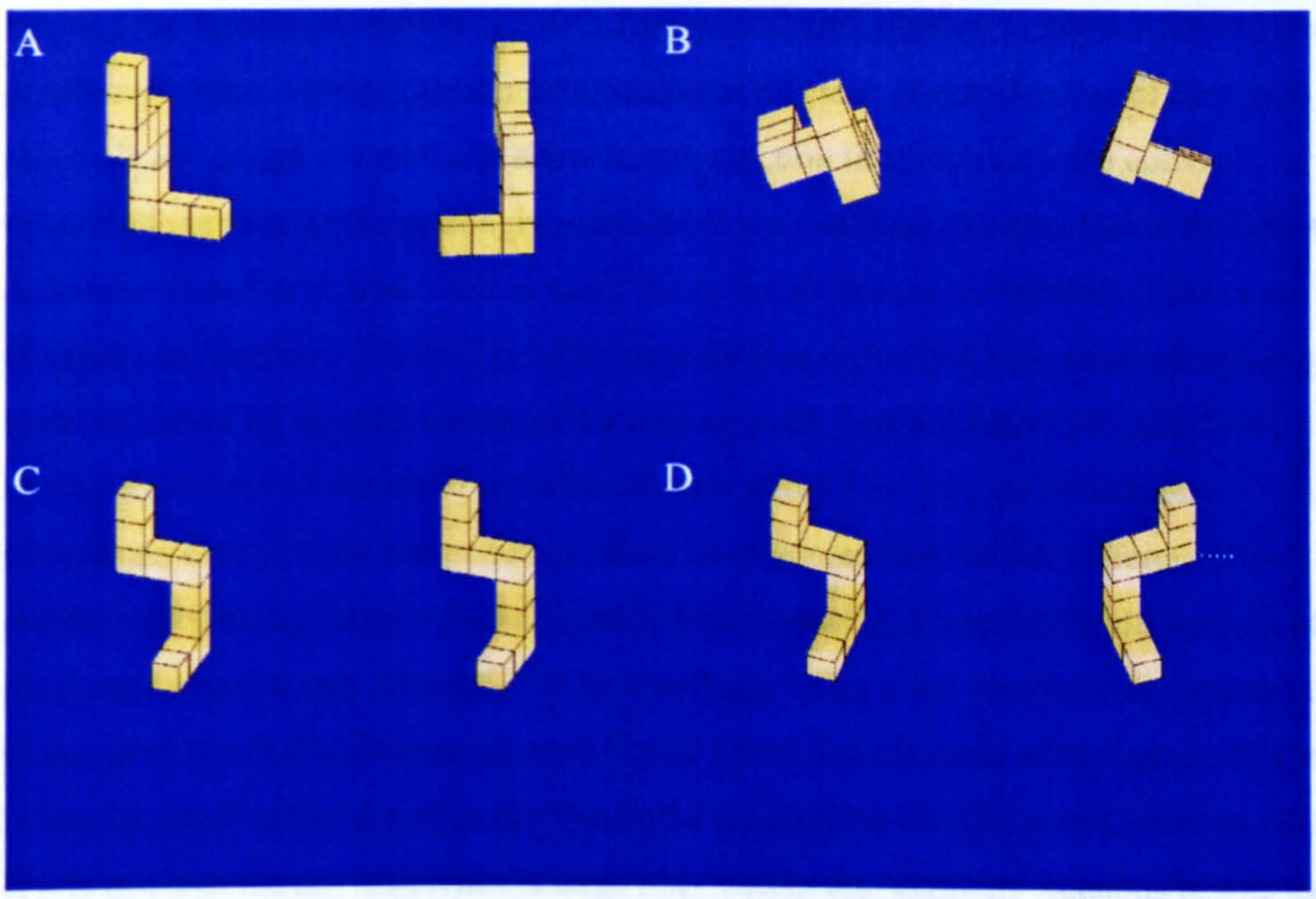


Figure 1: The top two images (A and B) are examples of the experimental condition. A: the right hand image is a rotated version of the left-hand image, so the response would be 'same'. B: the right-hand image is a rotated and mirror version of the left hand image, so response would be 'different'. The two images at the bottom C and D are examples of trials in the control conditions. C: the two images are identical (same). D: the two images are mirror versions of one another (different).

When this test of 3-dimensional figures is used, the rotations are known as "rotations in depth", because this task requires the subjects to rotate the figures imaginally, in 3-dimensional space. It is also important to note that, in relation to this rotational component, the reaction time to make the decision as to whether the stimulus figure is the same or different from the rotated options is a linear function of the increasing angular disparity between the two forms (Shepard and Metzler, 1971).

Generally, a majority of subjects find it difficult to perform the mental rotation task, regardless of gender, but men of all ages show superior performance, which stands true

whether the figures are shown in 2 or 3 dimensions, and whether or not the figures are familiar (Kimura, 1999). The computerisation of this task also makes no difference to this male advantage; women still show longer reaction times to reach the correct response than men do (this strongly supports, if not confirms, the conclusion that the sex difference found in mental rotation tasks lies in the rotational component of the task (Prinzel and Freeman, 1995). The effect size for this difference has remained stable over time (as shown by an examination of 14 studies, published between 1975 and 1992, testing adults and adolescents) and also remains stable over a range of cultures (Silverman et al., 1996). Nevertheless, some have argued that the sex differences in mental rotation may be only found in the 3-dimensional (i.e. more difficult) version of the mental rotation task (Stumpf, 1993). One study using a test representing figures in 2-dimensions (Spatial Relations sub-test, PMA) found that the male advantage on this test is less than half of that found in the Vandenberg and Kuse test (Linn and Petersen, 1985). If it is true that the sex difference is large only within the 'difficult' versions of this test, then men should also excel on 'difficult' 2-dimensional versions of it. One study, which lends support to this theory, is that done by Prinzel and Freeman (1995), which found that as angular disparity increased (90-180°) on a computerisation of the rotation task, so women tended to perform worse.

In a more recent study, Collins and Kimura (1995) developed a 2-dimensional mental rotation task that included increasing task difficulty. Subjects had to imagine how a figure, similar to a letter 'W' within a clock face, would look at a certain time (they were given 4 possible figures to choose from). This task was set at two levels of difficulty, smaller rotations at the easy level, and the difficult levels requiring larger rotations. The results of this study suggested that men excelled at the task at the more difficult level; the advantage for men at the easy level was $d = 0.43$, while on the difficult level this advantage stood at $d = 1.10$.

Others have argued that the sex difference on mental rotation tasks is influenced by other "performance factors". Goldstein et al. (1990), for example, pointed out that women do not necessarily make more mistakes on mental rotation tasks, but that women tend to

attempt fewer problems, as they work with more caution at these tasks. Furthermore, the time limit for the Vandenberg and Kuse test is 10 minutes; Goldstein and colleagues suggest that this time may not be long enough for women to work in. The authors also found that when computing the proportion of correct to incorrect responses in total number ("ratio scores"), in a sample of 33 men and 35 women, the sex difference disappeared. Therefore, from this they argued that the scoring of the Vandenberg and Kuse test, which acknowledged only the total correct, is somewhat insensitive to what may be significant, if subtle, variation. These conclusions were contradicted by another study (Masters, 1998), which used a larger sample size. Masters (1998) found that the sex difference stood up under unlimited time, as well as under a time constraint of 9 minutes. It was also found that the male advantage persisted in total scores as well as ratio scores (d ranging from 0.84 to 0.96). An interesting point, which Masters raises, is that attempting fewer items was associated with better performance. (Masters suggested that when Goldstein et al. (1990) found a smaller effect size for the rotation scores, it may be an artefact of the ratio scoring methods). Other studies also support the findings of Masters. The time limit question was addressed in studies by Resnick (1993) and Delgado and Prieto (1996), who found that on sample sizes of 88 men and 94 women, and 1400 high school students respectively, the time limit had no effect on the results relating to sex differences, and specifically no effect on the male superiority in this area. After computing a ratio measure for their mental rotation tests, Prizel and Freeman (1995) still found that men outperformed women. It is possible that other factors, like sex differences in processing of depth, have an influence on these 3-dimensional versions of mental rotation tasks. (For support of this possibility, see Kimura 1999, who argues that many unpublished studies show a female advantage in stereoscopic depth perception). Therefore, it is perhaps the case that while women perform worse than men on 2 or 3-dimensional rotation tasks, they may outperform men at some other aspects of 3-dimensional processing.

1.2.2.2 Spatial Visualisation

Spatial visualisation tests also tend to show a modest advantage to the male. The primary tests, which measure spatial visualisation ability are: the Embedded Figures Test (EFT),

the Block Design sub-test of the WAIS (BD), the Spatial Relations sub-test of the Differential Aptitude Test (DAT-SR) and the Paper Folding Test (PFT). The salient feature of all of the above tests is that subjects must imagine the relationship between whole forms and their parts, in addition, with the EFT; subjects must try to ignore the framework in which the pattern is embedded. In this case men may be performing better on this test because they are better able to ignore the complex framework and only concentrate on the simple pattern presented (Kimura, 1999; Witkin, 1967; see also male performance on the water level testl; WLT and the rod and frame test; RFT, spatial perception tasks, below).

1.2.2.3 Spatial Perception

Spatial perception tests also tend to demonstrate a moderate male advantage. This ability is usually measured by 3 common tests: the water-level test (WLT), the rod and frame test (RFT) and the Benton Judgement of Line Orientation test (JLO) (Voyer et al., 1995; Benton et al., 1983). In the WLT (which involves being presented with a series of pictures of jars, and being asked to draw a line to show where the water will settle, the subject in each case should draw a horizontal line, as water always settles at a horizontal level), the male advantage is standard across adults, children and university students, whether or not the subject has a scientific background. Kimura (1999) proposed that this task requires two elements for successful performance. Firstly, the subject must understand the rule that water always settles at a horizontal level, and secondly, the subject must ignore the background distraction of the tilted jar, to maintain horizontal perception. Therefore, it may be that men perform better on this test because they are able to ignore the background information (the tilt of the jar), and narrowly concentrate on the perception of the horizontal.

The RFT is similar to the WLT; it comprises a diamond shaped frame that is tilted at various angles, and a rod that must be set at a true vertical position within the frame. The JLO task also tends to show a male advantage (Benton et al., 1983; Woodard et al., 1998; Basso et al., 2000; Collaer and Nelson, 2002), but this task works a little differently;

subjects are asked to estimate the angular relationships between line segments by matching stimulus line pairs to an array of 11 lines forming a semi-circle. Collaer and Nelson (2002) found a large sex difference favouring males on the JLO task (d = 0.85). However, they found that in the 7 minutes allocated to complete the task, 96% of males and 84% of females completed the task with a minute or more to spare. Collaer and Nelson (2002) concluded that the sex difference on this task did not appear to result from differences in speed, but rather from differences in performance accuracy.

1.2.2.4 Spatial Memory

Sex differences can also be found in spatial memory, which is a combination of several mental processes: encoding, storing and retrieving information regarding route navigation, configurations and object locations (Kessels et al., 2001). Two spatial mnemonic processes work within spatial memory; spatial memory for routes and paths, or "spatial navigation" memory, and object location memory (or "spatial location" memory - Kessels et al, 2001). Spatial navigation tends to be the province of men, whereas studies on spatial location memory will tend to show an advantage for women.

Another major difference between spatial memory processes is between those memory processes that refer to directions and locations relative to the viewer (egocentric, also referred to as exocentric, deictic, body-centred, relative) versus processes that are externally referenced, that is, relative to landmarks or co-ordinates outside the observer (allocentric, also called geocentric, place, cue-based). This division is mainly based on the theory of "cognitive mapping". This theory proposes that the information from the environment is encoded, stored and processed in an allocentric manner (that is, like a "bird-eye view" or a map). However, it is possible that the initial encoding of environmental information takes place in an egocentric manner with later retrieval of this information to help recall to be processed allocentrically. Sex differences in spatial memory research have not yet approached these concepts of allocentric versus egocentric processing. Studies that examine sex differences in spatial memory have used tasks involving egocentric processing, with perhaps allocentric processing a later stage.

1.2.2.4.1 Spatial Navigation

The male advantage in the route learning aspect of spatial navigation has already been mentioned, and many studies have verified this advantage using simple pencil-and-paper tests (Galea and Kimura, 1993; Dabbs et al., 1997; Gibbs and Wilson, 1999; Beilstein and Wilson, 2000). These studies also have found that men and women seem to navigate in different ways. Dabbs et al. (1997) found that when directing an imaginary person through 4 town maps, men used geometric cues (i.e. direction and distance judgements), whereas women tended to use landmark cues.

An earlier study by Galea and Kimura (1993) also used the technique of directing an imaginary person through a 2-dimensional map of a fictional town, and came up with the same findings: men used geometric properties to direct, and women used landmark cues. Men also made fewer errors in this study, and needed fewer trials to learn the route. Further support for these findings comes from studies by Gibbs and Wilson (1999) and Beilstein and Wilson (2000); however, the studies named so far are somewhat limited, in that they do not reflect real-world route navigation. Two-dimensional maps do not allow participants in the study to travel a route egocentrically, and are not demanding of allocentric forms of reference (c.f. Dabbs et al., 1998). Also, closer practical knowledge of maps could be cited to explain the male superiority in these above cited studies.

In the light of these problems, several studies have tried using computer-generated 'virtual' environments, and again, the results showed a large male advantage (Moffat et al., 1998; Astur et al., 1998). Moffat et al. (1998) found that men were quicker and more correct at learning a route through a landmark-free "virtual maze"; even allowing for the males' extra experience with similar computer games, the male advantage remained (d =1.40). Sandstrom et al. (1998) compared performance of men and women on a virtual reality Morris water maze task, which was composed of distal visual cues within a trapezoidal room. When tested with the same cues, men and women showed no differences in performance. However, the removal or even the location variation of the

distal cues resulted in significantly impaired performance by women. It did not affect men in the same way, as the men showed an ability to make use of the trapezoidal shape of the room.

In their real world study Silverman et al. (2000) seemed to demonstrate the invalidity of the suggestion that male superior performance on navigation tasks could be due to their greater experience with map reading or computer games. The findings of Silverman et al's study were that men outperformed women in a "real-world" navigational task. Subjects in this study travelled through the woods with an experimenter, who took strategic compass readings at 4 points along the way, and from the end point of this journey, subjects had to travel back to the starting point by the most direct route. The number of steps taken by the subject was measured with a silent counter by the experimenter. It is possible that men took longer steps compared to women, however, this point was not adjusted for in the analysis. Men were found to have a significant advantage in this study. Schmitz (1997) supported these findings with the discovery that, in a maze arranged over 2 floors of a large building; girls of 10-17 years old were slower to find the exits than their male counterparts of the same age.

1.2.2.4.2 Object Location Memory

Object location memory is unique amongst the spatial tasks, in that the advantage is significantly female. Eals and Silverman in several studies in 1992 and 1994 found that women significantly outperformed men on a task of object location memory. This task involved 3 stages, which were (1) to identify the items that had been added to a 2-dimensional pictorial display of items, which had been previously been examined by the subject; (2) to find out which items had changed position on another previously studied picture; and (3) to recall the positions of objects in a previously seen office room (which contained objects that you would expect to find in an office, and also objects that you would not expect to see there). Eals and Silverman (1994) refer to (1) as object memory and (2) and (3) to object location memory. The results of this study were highly significant for a sex difference in this field; of 19 administrations reported by the authors,

only 7 did *not* show a female advantage (and of those 7, 6 were object memory, and not location, tasks).

Interestingly, when Alexander et al. (2002) used a modified version of the object location memory task, they found that for both men and women there were differences in object location memory, depending on where the objects were located. Both sexes tended to better recall objects at the periphery of the area presented, performing worse on recall of objects in the centre of the area. However, the major finding of this study was that women showed better object location memory for objects in the right visual hemisphere, compared to those in the left hemisphere. The same was not true of the men tested. One explanation for this, proposed by Alexander et al. (2002), was that the left hemisphere processing of spatial information facilitated the female advantage in object location memory. However, another explanation was suggested by Postman et al. (1998); that these differences could be extant because women use verbal strategies during object identification and recognition processing, which is governed primarily by the left hemisphere.

These suggestions of superior female performance in object location memory are given some support by two other studies, which demonstrated a large female advantage in their object location memory tasks ($d = 0.89$, Hill et al, 1995; McBurney et al., 1997). Hill et al. (1995) carried out a study using a task in which participants were supposed to put objects back in their correct locations in a room. McBurney et al. (1997) using a commercial game called "Memory", asked subjects to match up pairs with pictures of objects on them, while the cards are lying face down and no more than 2 pairs of cards are turned over at any one time. The female advantage in these studies was significant, and was apparently so under both intentional and incidental memory conditions (e.g. Alexander et al., 2002; Eals and Silverman, 1994; McBurney et al., 1997; Silverman and Eals, 1992).

1.2.2.5 Spatial Working Memory

Working memory refers to the process of information maintenance in moment-to-moment awareness (Baddeley, 1986). The process enables an individual to maintain an internal representation of a stimulus - "online", as it were to direct appropriate responses after the stimulus itself is no longer present. Working memory is considered to be a crucial cognitive function, a "gateway" function.

Working memory, the ability to maintain and update information in mind, is a key feature in most mental activities. This of course means that differences, however subtle, in working memory will have an impact on a broad spectrum of mental abilities. When looking at this construct from within a visuo-spatial framework, the ability to maintain a representation of a three-dimensional image whilst simultaneously imagining what it would look like if moved in space, or viewed from a different orientation would appear to be a classic example of visuo-spatial working memory. Furthermore, there have been no studies that have attempted to conceptualise sex differences in spatial perception, spatial visualisation or mental rotation within the framework of the spatial working memory, although this development in cognitive psychology has been around for about 20 years.

It was Baddeley and Hitch in 1974 that introduced the first 3-step model for working memory: 1.Central executive, controls attentional resources and organises thinking and generation of responses. 2. Phonological loop, maintains tracking of speech-based information, and also short-term storage. 3. Short-term storage and tracking of visuo-spatial information by the visuo-spatial sketch-pad

This model can be applied to either verbal or visuo-spatial working memory, depending on whether Phonological loop or visuo-spatial sketch-pad is activated. So we can see that, within this framework, mental rotation and spatial perception tasks require both maintenance of spatial information (short-term storage on visuo-spatial sketch pad) and manipulation of this information (central executive). According to Loring-Meier and Halpern (1999), a more specific examination of cognitive processes on these mental rotation and spatial perception tasks could be gained by conceptualising them in the

working memory format. The study by Loring-Meier and Halpern (1999) aimed to explore sex differences in multiple components of visuo-spatial processing, developing a number of tasks, which assessed: (1) retrieval of information about letter-shape from long-term memory into the visuo-spatial sketch pad (generation). (2) Short-term manipulation and decision-making of the image (maintenance). (3) Maintaining the position of a blackened square and arrow in memory while scanning an array to determine if the arrow points to the original position of the square (scanning). (4) Matching identical and mirror-reversed two-dimensional bars (transformation or rotation component).

Loring-Meier and Halpern reported that men responded more quickly than women across the range of tasks, and they also found no sex difference in accuracy, which was contrary to what they had expected. This result does not support their suggestion that sex difference in visuo-spatial working memory is separated across the tasks. From their actual results, they concluded that the speed of processing is key to sex differences in this area. It is not likely, then, that we will find sex differences in any of the single components of working memory. It should be noted here, though, that their study used not the original version of the theoretical framework for visuo-spatial working memory, but a version of it, developed for the elderly by Dror and Kosslyn (1994). These authors had proposed 4 components to image processing, namely generation, maintenance, scanning and transformation. So, the Loring-Meier and Halpern (1999) study was not strictly based on a working memory task, and more sophisticated tasks would probably aid further study in this field.

There is also the point to be considered, that 'mental rotation' and 'spatial perception', as sub-categories within the broad spectrum of 'spatial abilities', may be fine enough distinctions; it could be that there is no real need for finer distinctions than these.

1.2.2.6 Influence of Mental Rotation on Sex-Dimorphic Motor Tasks

Many studies have shown a large male advantage on gross motor tasks, for example, throwing and catching balls, showing an advantage in aim and interception skills (d=1.97; Watson and Kimura, 1991; Lunn, 1987; Halpern, 1997). Fine motor tasks, on the other hand, show a significant female advantage, and involve the co-ordination of a series of fine movements of the fingers, such as on the purdue and grooved pegboard tasks (dominant hand d = 0.52, non-dominant hand d = 0.45), assembly measure (d = 0.53; Kimura, 1999). Factors like finger size, speed and sports history, strength or physique, or most forms of spatial cognition have no influence in this area. So, could the male excellence in rotational ability possibly be a factor of influence? For example, the large male advantage in a throwing and interception task was un-correlated with greater scores on tests measuring spatial perception and a "View-finding test", in which subjects were required to imagine how an object placed in front of them would look if viewed from alternate perspectives in an array (Watson and Kimura, 1991). This study may support the theory that sex differences in motor skills are separable from other spatial skills.

1.2.2.7 Mathematical Ability

In terms of sex differences, though mathematical ability is often referred to as within the domain of spatial abilities, mixed results are usually reported. Generally speaking, girls tend to outperform boys where mathematics are concerned within the school period, so within the framework of academic achievement (UK school period = 4-16 years, Kimura, 1999; Jenson, 1988). Conversely, when examining the findings of mathematical aptitude tests, which are not within the framework of academic ability, and do not rely on academic input, men are the better performers on reasoning tests and mathematical problem-solving. However, on these same tests, women perform better at computation and calculation tests (*d* between 0.20 to 0.60; Benbow, 1988; Geary, 1996; Geary et al., 2001; Hyde et al., 1990; Kimura, 1999). Although these sex differences are smaller in non-white ethnic groups, they do hold true over a range of cultures (e.g., Jenson 1988), but there does seem to be a suggestion of decline in sex differences over time and with

age (Feingold, 1988). It is not clear, though, why sex differences appear in the direction that they do, on aptitude rather than academic tests.

So, why are men outperforming women on mathematical problem solving? Could this be related to their superior performance on spatial tasks? It has been suggested, by the findings of several studies, that performance on mathematical reasoning tests could be related to performance on mental rotation tasks (which may explain why researchers sometimes include mathematical ability under the umbrella term of "spatial ability"). Johnson (1984) found that male superior performance in solving algebraic problems was significantly related to spatial abilities, but less so to IQ. Casey et al. (1997), using the American Scholastic Aptitude test (SAT-M), reached the same conclusion, finding that excellence on 3-dimensional mental rotation tasks was linked to excellence in mathematical ability. They also found that a positive attitude to mathematics played a part. Geary et al, (2000) suggests that the male advantage on mathematical aptitude tests shows a superior capacity for manipulating spatial representations of the information in mathematical problems (e.g. algebraic problems), even when the problem has been verbally presented. However, Kimura (1999) disagreed; she argued that the male advantage in mathematical aptitude is due to an ability to translate verbally presented problems into numerics.

Another explanation could be that the male advantage at mathematical problem solving is related to greater computational fluency (that is, the greater ability to retrieve mathematical rules from long-term memory). In an effort to explore these various and contradictory arguments, Geary et al. (2000) undertook a study in which they gave 113 men and 123 women (mean age: 19 years) mathematical reasoning tests (Necessary Arithmetic and Mathematical Aptitude sub-tests from Ekstrom et al's, 1976 battery), arithmetic computations (Simple subtraction, Complex subtraction and Complex addition from Ekstrom et al., 1976), IQ (Raven's SPM) and the Vandenberg and Kuse mental rotation test. The findings, using structural equation modelling, were that the male advantage on mathematical reasoning tests was mediated by a male advantage in computational fluency *and* mental rotation tasks. However, covarying for IQ, mental

rotation was found to be the strongest mediator, supporting the theory that mental rotation superiority strengthens the advantage in mathematical reasoning, perhaps by acting in visuo-spatial working memory to manipulate the information in multi-process arithmetic operations.

1.2.2.8 Developmental Occurrence of Sex Differences in Spatial Cognition

Another area in which research has produced progress is in addressing the question of when cognitive sex differences in spatial abilities first emerged. Maccoby and Jacklin (1974) argued that sex differences, particularly in spatial abilities, were not apparent until after puberty. Social psychologists interpreted this to suggest that changes in social roles at puberty were responsible for the sex differences, whereas those with a more biological perspective thought that hormonal changes at puberty might be responsible.
Subsequently, it was noted that different types of tasks were typically used with children versus adults, and that the type of task used most often with children (disembedding tasks) showed small sex differences in both children and adults. When children were given mental rotations tasks or spatial perception tasks they showed more substantial sex differences. Clearly, here we have a question, which it is very pertinent to discuss.

There are several studies which report a male advantage from as young as 4 years old, on tasks like replicating the spatial arrangements of objects in the Block Design sub-test; the Mazes sub-test of the Weschler Intelligence Scale for Children (WISC) and replicating three-dimensional Lego models (Linn and Petersen, 1985; McGuiness and Morley, 1991; Voyer et al., 1995). Rosser et al (1984) reported that tasks involving matching a 2-dimensional figure to its mirror reflection from a series of rotated foils favour boys of 4-5 years old.

It must of course be borne in mind that we do not know how far such tasks may represent the capacity of "imaginal rotation"; "true" tests of mental rotation tend to show male advantage from the age of about 8 (e.g. Kerns and Berenbaum, 1991). The meta-analysis

conducted by Voyer et al. (1995) showed a significant male advantage in older children (no minimum age was specified, but the maximum age was 13). For adolescents aged 14-18, sex differences were found on the mental rotation tests, the spatial-relations sub-test of the PMA and the spatial-relations sub-test of the DAT. Tests measuring spatial visualisation showed no sex difference under the age of 18. In an earlier study, Nebot (1988) tested 50 boys and 50 girls (aged 8 years), on the children's embedded figures test and found sex differences favouring boys. Unfortunately, there are no data on early sex difference on the JOLO test.

A number of studies have also reported boys of 3 to 5 years old to outperform girls in distinguishing mirror reversals of triangles from identical triangles, a task which may comprise a rotational component (Cronin, 1967). Levin et al. (1999), developed a task in which the child had to mentally integrate two parts of a shape, and match this to the correct shape in an array of other shapes. By the age of 4 years and 6 months, despite a small effect size of $d = 0.25$, there was a significant male advantage. The results of this study support Levin et al.'s theory that the earliest presentation of sex differences in visuo-spatial functions would involve mental rotation. The authors also argue that, as many spatial tests are very difficult for young children to perform, it is not entirely surprising that there has not been much evidence for Levin et al.'s theory.

To summarise, then, the developmental trajectory of sex differences in the three main categories of spatial abilities that show a male advantage, demonstrates an earlier onset of sex differences for the mental rotation tests (at around 4 years), pubertal onset for differences in spatial perception (13-18 years) and childhood onset (at around 8 years) for differences in spatial visualisation.

1.2.3 Verbal Abilities

1.2.3.1 Verbal Fluency

From early childhood onwards, girls are found to have larger vocabularies than boys, begin to speak and articulate sooner, and spell and read better than boys (Kimura 1999). In fact there is a common belief that women have better verbal skills than men do. This is one of the many stereotypical sex differences that depend on cultural preconceptions, although there are findings from various studies, which seem to support it. For example, when Flannery et al. (2000) carried out an analysis from a large study of 32,000 white and black children, they found reading disabilities to be to be only half as common amongst the girls, compared to the boys.

There does not seem to be any sex differences on tests of vocabulary and verbal IQ (although IQ tests are generally designed to eliminate these differences – Kimura, 1999), but from adolescence onwards women do show a decided advantage in one aspect of verbal ability, which is verbal fluency. Verbal fluency tests, as well as measuring verbal ability, are also used to assess the integrity of central executive functioning. According to Baddley and Hitch's (1974) Working Memory Model, verbal fluency depends on rapid intrinsic response generation, and therefore is demanding of central executive resources to organise thinking, and shifts between strategies, and to access retrieval strategies (Abrahams et al., 2000; Troyer et al., 1997).

Verbal fluency tests usually involve subjects saying as many words as they can, within a time restraint, starting with a certain letter, or within a certain category. The first type of fluency, known as "phonological fluency", involves word generation based on phonetic information, e.g., words beginning with 'S'. The second type of fluency, category fluency, involves, for example, recalling "all the words you can from the category 'Vegetable'" – i.e., this type of fluency demands the use of semantic strategies. Above this basic level, there are also tests which require a higher order of semantic exemplars, for example, asking a subject to generate and list words which mean the same as "soft".

Access to, and retrieval of synonyms may demand more of semantic and executive retrieval skills, than the demands made in category fluency. Verbal fluency tests also demand activation of the phonological loop, which maintains short-term storage of cue letters or words (Miller, 1984).

To examine the sex differences in this area, then, the female advantage on letter fluency is not that large (d = 0.3; Hyde and Linn, 1988), and the advantage on category fluency is moderate (d = 0.5; Acevedo et al., 2000). In a study by Lewine et al. (2000), no sex differences between men and women were reported at all in verbal fluency, either letter or category. Hyde and Lynn (1988) have argued that the sex difference in verbal fluency is so small that it is should be regarded as non-existent. However, in a study similar to that of Lewine et al (2000), in a group of males (n = 100) and females (n = 100), Hyde and Lynn (1988) found a female advantage in both category fluency (d =0.28) and letter fluency (d =0.49). Hines (1990) found a large sex difference favouring females on synonym fluency. There are many meta-analytic and empirical studies involving large sample groups, which show that women have a significant advantage on both category and letter fluency. The average effect size across these studies is d = 0.3 for letter fluency and d = 0.5 for category fluency (Capitiani et al. 1999; Herlitz et al. 1997; Laws, 1999; Loonstra et al. 2001; Mann et al. 1990; Sumerall et al. 1997). Herlitz et al. (1997) used a large sample size (the largest to date) of 470 men and 530 women (35-80 years), all of whom were randomly selected from a Swedish city, and the authors found that although age was also a factor in performance (performance decreasing with increasing age), the advantage was consistently towards females (d = 0.35).

The female superiority in verbal fluency is established, but women also may show an advantage on tasks such as story recall, word recall and word recognition. More and more studies are reporting that women have superior episodic memory (that is, the autobiographical record of information and events in individual experience encoded in specific temporal-spatial context, tests of which comprise encoding and retrieval components in memory), and more specifically, show an advantage in verbal episodic memory (Herlitz et al., 1999; Herlitz et al., 1997; Lewine et al., 2000). On many common

neuropsychological tests, which measure verbal learning, women are reported to outperform men (for example, on the REY Auditory Verbal Learning Test and the California Verbal Learning Test (CVLT; Kramer et al., 1988). On the CVLT, Kramer (1988) reported that women tended to use a "semantic clustering strategy" (the technique of grouping items according to semantic categories during recall of items). Kramer et al., in 1997, using the children's version of the CVLT on a group of 401 boys and 410 girls (5-6 years), replicated their adult findings when they reported that the girls scored higher than the boys on immediate and delayed recall (although the effect size was fairly small, d = 0.27 to 0.30). Girls appeared to use the semantic cluster strategy in this study. Also, the boys in this study made more false positive errors, being more susceptible to interference. Another study to suggest that female verbal memory advantage is attributable to efficient retrieval processes was that by Basso et al. (2000), which used the Verbal Paired Associates test of the Weschler Memory Scale, or WMS-II (in this test, participants are shown 2 words as a pair, and in the 4 recall trials, they are shown just one of the word pair, and must recall the other word).

In a study by Herlitz et al. (1999) testing men and women with a series of episodic memory tasks (abstract word free recall, concrete words free recall, pictures free recall and recognition), it was found that women outperformed men on most of them. It should be mentioned here that the authors provided no criteria for classification of the tasks used. However, Lewin et al. (2001) carried out a similar study, but added new tasks to measure visuo-spatial episodic memory ("cube task" involving depiction of coloured blocks in a cuboid structure with later recall of which blocks were coloured in a plain cuboid, Rey Oesterrieth complex figures test and route learning and recall). The results showed that, while women outperformed men on face recognition and object recall (as previously discussed), men did perform better on cubes and key task, which measured visuo-spatial episodic memory. So, Lewin et al. (2001) suggested that women excel in those episodic memory tests where the material can be verbalised. It was also found that, after covarying for verbal fluency performance, this effect still remained; the authors pointed out that it was not possible to explain the female advantage on episodic memory tests by verbal fluency excellence alone, though, when the data were factor analysed, it

was found that there was a contribution of greater verbal fluency skills, to the advantage on episodic memory tasks.

Thus, it would appear that women do outperform men on verbal learning and memory, and that this sex difference can be observed from as early as 5 years of age (e.g. Kramer et al., 1997).

1.2.4 Cognitive Inhibition

Cognitive Inhibition refers to the ability to inhibit a response to an obvious stimulus (counting forwards, naming colours) in favour of a less obvious stimulus (counting backwards, naming the colour of the ink rather than reading the ink word).

It has been hypothesised that sex differences in cognitive abilities may also extend to cognitive processes of automatization and inhibition of responses. Broverman et al. (1968) hypothesised that women would outperform men on those perceptual motor tasks which prompt an automated response, while men would outperform women when the task requires a response to less obvious stimulus attributes (like inhibitory perceptual restructuring tasks), whilst inhibiting immediate responses to obvious stimuli. The authors also suggested that these sex differences may reflect differences in relationships between adrenergic activating and cholinergic inhibitory neural processes, which, in turn, are sensitive to the sex hormones, androgens and estrogens.

However, these hypothesised differences also relate to the parental investment theory, which proposes an evolutionary approach to these differences. Bjorklund and Kipp (1996) suggested a theory in contrast to that of Broverman et al. (1968), which was that, in prehistoric times, women had more pressure to inhibit their social and sexual responses (which could be maladaptive), and that the results of this could be the enhancement of inhibitory abilities in women, in some areas.

Many studies in the area of sex differences since the 1960s have used the Stroop test, designed to explore cognitive and behavioural inhibition. This test uses words printed with coloured ink to assess this cognitive function (particularly cognitive interference), and can be used as a screening instrument, or part of a battery of tests for screening frontal and executive brain function.

Cognitive interference occurs 'when the processing of a specific stimulus attribute impedes the simultaneous processing of a second stimulus attribute' (Zysset et al, 2001). Using the coloured words of the Stroop test is an example of this technique. A colour name such as 'RED' is presented in black ink, and the subject reads the word with no difficulty. If the word 'RED' is shown in blue-coloured ink, the subject will have no more difficulty with it than with black ink. However, if the subject is asked to name the colour of the ink in which the word 'RED' is printed (i.e. blue), the subject will have more difficulty. Thus, the colour of the ink does not interfere with the reading of the word, but reading the word does interfere with naming the colour.

Therefore, the Stroop test requires the inhibition of competing responses (See MacLeod, 1991 for a review of the Stroop task). The longer it takes to name the colour or word, the more interference is present, and the more difficulty there is with inhibition. Thus, slowed performance on this task is interpreted as difficulty with resisting interference, a cognitive function that is associated with frontal cortical integrity (Mesulam, 1987).

Since the emergence of the automatic-controlled distinction in cognitive psychology, the Stroop test has become more important, because it appears to access an automatic process (word reading) against a controlled and conscious process (colour naming). In other words, this test demands an active inhibition of a learned response, in favour of a voluntary response. However, in terms of sex differences, the Stroop test has not yielded consistent results. One study found a male advantage (Owens and Broida, 1998), some studies have found a female advantage (Mekarski et al., 1996; Sarmany, 1977), and Daniel et al. (2000) found no sex differences on this test at all. Response modality has been hypothesised as a possible explanation for these inconsistencies; e.g. the oral

response version of the Stroop test carried out by Daniel et al., 2000, found no sex difference, but Owens and Broida carried out a manual response version, and elicited a sex difference in favour of men.

Prepulse inhibition (PPI) of the startle response is another way to examine the effects of inhibition focussing more on stronger automatization. As PPI is not learned, and is therefore more related to brain differences, it is a valuable tool in assessing inhibition in men and women. PPI has shown reliable sex differences in healthy subjects, with women demonstrating less PPI than men (Blumenthal and Gescheider, 1987; Ornitz et al., 1991; Swerdlow et al., 1993, 1995, 1997, 1999, Abel et al., 1998; Kumari et al., 2003). There is evidence of menstrual cycle effects in PPI (Swerdlow et al., 1997), with maximum PPI ocuring 1-7 days after the last (self-reported) menstrual period. Healthy women however, have been found to show less PPI than men even when tested during the early follicular phase (days 1-7) of the menstrual cycle (Abel et al., 1998; Kumari et al., 2003).

Thus far, no one has tested the more general hypothesis of stronger automization in women and stronger inhibition in men. This could be in the future a fruitful area of sex difference research.

1.3 Cerebral Hemisphere Lateralisation

1.3.1 Sex Differences in Structure and Function

Cognitive dimorphism could also be related to functional or structural brain differences between men and women. There are structural variations in Broca's region and dorsolateral prefrontal cortex, which are associated with verbal functions (Harasty et al., 1997; Schlaepfer et al., 1995), and regions of the corpus callosum, which may suggest greater inter-hemispheric processing in women (Allen et al., 1991). A recent study has also demonstrated greater leftward asymmetry in the inferior parietal lobule in men, which may subserve the male advantage on spatial processing (Frederiske et al., 1999).

Studies using magnetoencephalography (MEG) show greater right hemispheric lateralization as reflected in the size of the superior temporal gyrus in men compared to women (Reite et al., 1995).

Several studies have suggested that women have bilateral representation of function for both verbal and non-verbal abilities, while men have greater hemispheric specialisation (Harshman and Remington, 1976; McGlone, 1980; Kimura and Harshman, 1984). Kimura (1987) with reference to studies on people with lesions suggests that women have greater focal language organisation in the left hemisphere. Evidence for these findings comes from the severity and nature of cognitive deficits following stroke or other brain lesions (McGlone, 1980) and a few experimental studies using tachistoscopic or dichotic listening techniques to selectively present material to a single hemisphere (Harshman and Remnigton, 1976; Bryden, 1979; Kimura and Harshman, 1984).

Great interest in the corpus callosum (the white matter tract connecting the two cerebral hemispheres) has arisen from the findings of sex differences studies in hemispheric specialisation (Witelson, 1990, 1992; de Lacoste 1990). Aboitiz et al. (1992) found greater interhemispheric connectivity connected with greater callosal size. It has been suggested that morphological sex differences in callosal size could help the interhemispheric communication in women's brains, and that this may be crucial to higher performance. Davatzikos and Resnick (1998) carried out a magnetic resonance imaging study, the results of which showed a significant sex difference in corpus callosum size, which reflects greater interhemispheric connectivity in women.

This line of thought was further supported by the discovery that cognitive performance was positively affected by the bulbosity of the corpus callosum in women, but not in men. From these findings, we can see that greater or lesser interhemispheric connectivity has different implications for cognition in women than it does for cognition in men.

Hines at al. (1992) found that verbal fluency performance correlated positively with the area of the splenium and with the area of a posterior callosal factor defined by the splenium in a group of 28 women (aged 20-45 years). Hines and colleagues postulated

that a larger corpus callosum is associated with better interhemispheric transfer of information, which contributes to verbal fluency. They also found that the posterior callosum, in particular the splenium also correlated negatively with language lateralization. Witelson in 1989 found that left-handed individuals had larger corpus callosum than right-handed individuals. Witelson suggested that the brains of left-handed individuals are similar to the female brain with respect to the size of the corpus callosum.

These findings suggest that the degree of interhemispheric connectivity may have different implications with regard to cognitive performance for both men and women.

1.3.2 Sex Differences in Cerebral Lateralisation

Neurocognitive sex differences have been suggested to relate to differences in neural hemispheric specialisation, or lateralisation. Clusters of functions within specific hemispheres of the brain are consistently reported in the literature. For example, several studies have reported that verbal and fine motor functions are predominantly located in the left hemisphere, and visuo-spatial functions such as mental rotation and JLO are dominant in the right hemisphere in right-handed individuals (Geschwind and Galaburda, 1985a and b; Lezak, 1995). The identification of the language dominant hemisphere, or whether language functions are insufficiently represented in either hemisphere, is of crucial importance in the assessment of normal neuropsychological functioning (Lezak, 1995). It is suggested that this pattern of specificity in the brain varies as a function of important individual differences, specifically, sex and handedness. Together with the information on sex differences in cognitive performance, it is assumed that men perform better than women on certain spatial tasks (e.g. mental rotation, JLO) due to their greater lateralization for these tasks, in the right hemisphere (McGlone, 1980). Conversely, women tend to perform better than men on some verbal tasks (verbal fluency) because these functions are bilaterally represented in the brain.

One theory postulates that impaired spatial ability in women may be a consequence of bilateral representation of language functions that interferes with the functioning of mechanisms necessary for efficient spatial functioning (the hemisphere displacement theory, Levy and Heller, 1992). This theory predicts that men should show hemispheric advantages on specific cognitive tasks, while the same is not expected from women. In contrast, a theory put forward by Buffery and Gray (1972), maintains that spatial functions are bilaterally represented in males, which results to better spatial function, whereas lateralization of verbal functions in women is responsible for their superior performance on verbal tasks. This theory however, fails to specify the precise verbal task involved. Furthermore, this hypothesis predicts that women should show hemispheric advantages on specific tasks, whereas men should not, whilst another theory suggests that

bilateral representation of verbal and spatial functions is a general advantage across tasks (Gur et al., 2000).

Studies that have examined sex differences in cerebral laterality have predominantly employed measures of handedness as well as visual field tasks, dichotic listening tasks, and dual task paradigms. The basic idea behind studies that use these measures as markers of hemispheric dominance is that individual differences in the extent of right-or left sided usage of motor and sensory functions provide indices of differential hemisphere utility and organisation (based on the fact of contralateral interactions between brain hemispheres and motor and sensory functions).

A measure of hand preference is notably the most common and economical measure of cerebral dominance; however, information from current brain imaging studies have argued that this tool is a poor correlate of actual brain asymmetry (e.g. Good et al., 2001; Knecht et al., 2000). Geschwind and Galaburda, (1985a and b) have suggested that among left handed individuals, the normative pattern of leftward hemispheric dominance for language, and the rightward dominance for spatial functions in right handed individuals, show a reversed pattern of lateralized functional dominance. Clearer evidence is observed in the extremes of cognitive competencies. There are more non-right handers among individuals with several types of mental retardation and impaired verbal and reading abilities, as well as a higher percentage of mathematically gifted individuals. However, these mathematically gifted non right-handers also tend to be men (Lezak, 1995). Left-handed men have been found to be over-represented in mathematically advanced adolescents (Benbow, 1988).

With regard to cognitive tasks that show sex differences, non right-handed men have been reported to show enhanced verbal and perceptual speed skills but impaired visuo-spatial skills (performance similar to right handed women); whereas, like right-handed men, non right handed women tend to exhibit the reverse pattern: improved visuo-spatial functions and poorer verbal skills (Gordon and Kravetz, 1991). This pattern of findings have been reinforced by Pezaris and Casey (1991) who argue that right-handed women

who were competent in maths and sciences and obtained high scores on the mental rotation test may come from families consisting of non-right handed immediate relatives, which suggests that familial sinistrality may enhance sex and handedness effects on visuo-spatial functions. However, to date, no study has replicated these findings.

In a recent study, Eviatar et al. (1997), tested the performance of 74 right-handers (35 men and 39 women) and 32 left handed individuals (17 men and 15 women) on tests of three putative components of cerebral laterality; (1) a consonant-vowel-consonant (CVC) identification task in which subjects are presented with CVC syllables in each unilateral visual half field and bilaterally where the same CVC is presented in both fields (the aim is to identify the letters making up the stimulus) to measure differences in hemisphere strategies use, (2) a nominal and physical letter-matching task presented bilaterally to index callosal flexibility, and (3) a chair identification task where pictures of two chairs are presented tachistoscopically, one in each visual field (the subject is required to identify these chairs in arrays of 12 trials) to measure hemispheric arousal. For task 1, left-handers showed smaller performance asymmetries than right-handers, suggesting more efficient right hemisphere (RH) functioning in left-handers. This effect was stronger in men than in women, which suggest that more left-handed men use a strategy closer to a RH mode of processing. The data from task 2 suggested that the left-handers had less callosal flexibility and the data from task 3 indicated that left-handers comprised individuals with more aroused RH's. Sex and handedness did not interact in these final two tasks. Overall, the authors concluded that handedness affects the hemispheric organisation of men, but not women, and that handedness has an effect on hemispheric lateralization and interhemispheric interactions beyond that of sex.

The use of hand preference as a measure of hemispheric organisation and related variables, such as sex, remains unresolved and will do so for as long as researchers insist on investigating a substantially skewed trait. Left-handedness occurs in approximately 10% of the population, and thus a large effect size or a very large sample size is needed to offset this base rate in order for tests of any hypothesis regarding handedness to be meaningful. Furthermore, it is often argued that deviations from left hemisphere

language dominance in left-handers must be related to neural pathology, or some kind of "developmental perturbation". The reasons why language processes are dominant in the left hemisphere in most people is yet unknown, whilst any knowledge that is available is biased towards pathological states (for example, schizophrenia. This is discussed in chapter 2). In actual fact the exact variability of language lateralization in the population overall is unknown.

Recently Knecht et al. (2002) employed Doppler ultra–sonography coupled with an intracarotid amybarbital procedure during a word-generation task in 188 healthy, strongly right-handed individuals. The authors reported no sex differences in language lateralization but found right hemisphere dominance in over 7% of subjects (1 in 3), which suggests that a typical language dominance in healthy right handed individuals is more common than previously assumed.

More consistent results regarding sex differences in cerebral laterality have been found in an exhaustive meta-analysis of studies using laterality tests in the auditory, visual, and tactile modalities (e.g. dichotic listening and tachistoscopic studies), which suggest a consistent but weak population level sex difference such that men show greater lateralization (Hiscock et al., 1994; Hiscock et al., 1995; Hiscock et al., 1999). These studies established the number of reports that have provided information on sex differences; the proportion of these yielding sex differences according to stringent criteria (for example, the nature of modality, presentation format of stimuli-unilateral or bilateral, sample composition – child or adult, sex by modality interactions and direction of significant results); and whether men were more likely to show greater lateralization. From approximately 940 experiments, 65 yielded significant sex differences pertinent to the hypothesis of sex dependent differential hemisphere laterality (e.g. McGlone, 1980), and 80% of these supported the hypothesis, compared to 20%, which did not. These conclusions corroborate those of Voyer (1996) who concluded that there were very small sex differences (approximately 0.6 standard deviation units between the effect of men and women) reflective of greater lateralization in men in visual and auditory but not tactile modalities. These differences were reported for tasks using verbal (commonly the

presentation of vowel-consonant pairs) or nonverbal stimuli (commonly the presentation of polygon figures). Recent evidence that have examined task-specific sex differences in laterality reveal patterns at variance with the conclusions of Hiscock et al. and Voyer (1996).

In dual-task paradigms, a putative right-hemisphere or left hemisphere task is coupled with a motor task (such as hand tapping), which disrupts the simultaneous performance on one hand more than the other. This asymmetric interference is attributed to differential demands on each hemisphere, given an index as to which hemisphere is being 'activated'. An analysis of sex differences in dual-task paradigms is important in order to control for the confounding effects of attentional biases in auditory or visual field tasks. Attentional biases may alter actual asymmetry because processing resources are differentially allocated laterally (so greater processing on one side may measure fewer resources for perception of the stimuli on the other). A sex difference in laterality may then be an artefact of sex related differential biases and strategy utility. In dual task paradigms, left and right hands are tested separately, thus an attentional bias may influence allocation of resources between two concurrent tasks but have no effect on the asymmetry of interference.

In a review of studies from sex neuropsychology journals, Hiscock et al. (2001) found that out of 51 experiments, 23 demonstrated a significant sex difference, though only 5 of these showed unambiguous sex differences of greater hemispheric specialisation in males. These differences could not be explained by sex differences in gross and fine motor co-ordination. The authors concluded that there is a very weak, but reliable, population-level sex difference in human laterality consistent with McGlone's (1980) hypothesis.

Further investigating the role of response biases due to attentional factors, Voyer and Flight (2001) conducted 4 experiments where strategies during dichotic-listening tasks were manipulated (free recall of consonant-syllable pairs, ordered recall, focussed attention on a specified ear, detection of binaural probe presented dichotically) and found

that once attentional factors were controlled, sex differences in laterality were easily detected.

To summarise, although findings from studies support the hypothesis that female brain function is less lateralized compared to men, the size of this difference appears small and the notion of sex differences in cerebral organisation is still much debated (Kolb and Whishaw, 1995).

1.4 The Neural Basis for Sex Differences in Neurocognitive Performance

1.4.1 Overall Brain Structure

A number of studies have consistently reported sex differences in overall brain size which appears to be the biggest structural difference between men and women. In general men are reported to have approximately 10% larger brains compared to women after having controlled for weight and height differences (e.g. Goldstein et al., 2001; Good et al., 2001; Nopoulos et al., 2000). Some have argued that this sex difference in global brain volumes is an artefact of differences in the ratio of grey to white matter. Two studies have demonstrated that men have proportionately greater white matter volumes than women (Filipek et al., 1994; Gur et al., 1999). On the other hand, Reiss et al. (1996) reported that although boys had a 10% larger cerebral volume than girls, an increase in grey matter was the primary contributor to larger brain volume in boys. DeBellis et al. (2001) examined the brains of 118 healthy children and adolescents (matched for IQ) from MRI images and found that males had more prominent age-related grey matter decreases and white matter and corpus callosal volume increases compared to females. DeBellis et al. argued that grey matter decreases could reflect dendritic pruning, whilst white matter increases could be due to myelination, increases in axonal size or glial cell proliferation. It is possible that, to some extent, observed overall brain volume change is actually reflective of corresponding changes in adjacent white matter concentration rather than grey matter (Penhune et al., 1996). Two recent studies have shown no influence of

grey to white matter ratio on the overall male-favouring difference in cerebrum size (Good et al., 2001; Nopoulos et al., 2000).

In an analysis of 465 adult brains acquired by structural MRI, Good et al. (2001) reported the mean absolute and relative grey to white matter volume ratio as 1.89 and 1.82 for men and women respectively, which does not demonstrate a significant difference. The functional significance of this difference in brain size has generated much debate. Initially, it was thought that the difference in overall brain size may be related to specific functions such as superior mental rotation ability in males; however, these functions have been found to show their own neural sexual dimorphism that may be unrelated to global volumes. Instead, some have argued that sex differences in brain size may reflect differences in general intelligence, with the politically distasteful implication that men are more intelligent than women on the basis of their larger brains (Lynn, 1994).

Although there is a modest correlation between brain size and intelligence (e.g. Andreasen et al., 1993), most studies of differences in global brain size matched men and women for IQ and still reported differences. Reiss et al. (1996) showed that in healthy children, a best curve fit of the association between IQ and cerebral volume suggested that IQ increased with larger cerebral volumes up to a point, then reached a plateau, and then decreased with the largest volumes. The lack of findings with regard to the association between IQ and sex differences in overall brain size may partly be due to the lack of sex differences reported in IQ at the behavioural level.

1.4.2 Neural Correlates of Mental Rotation

Functional and structural imaging studies examining the neural substrates of visuo-spatial functions have focussed predominantly on mental rotation tasks (both two and three dimensional). The mental rotation task is a complex task that requires the imagined motion of visual objects with the ultimate goal of identifying them as the same, or different. This multifaceted task would presumably involve several cognitive or mental operations, including encoding of the visual images, rotating them, judging whether they

are the same or not, making a discriminatory motor response etc. Also, other general processes would be involved such as attention and visual tracking.

Some studies examining patients with brain lesions have reported impairments in mental rotation after damage to the posterior right hemisphere (Ratcliffe, 1979, Farah and Hammond, 1998, Dittuno and Mann, 1990). Whereas others have reported impairments in mental rotation after lesions to the posterior left hemisphere, (Mehta and Newcombe, 1991). Overall it seems feasible to conclude the involvement of the parietal lobes in mental rotation. In general, studies using functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) have singled out the parietal cortex as the cortical area most consistently and prominently activated during task performance on the mental rotation task (adapted from the Shepard and Metzler's three dimensional figures) and tasks depicting two-dimensional representations of rotated alphanumeric figures, rotated abstract figures and rotated hands (Barnes et al., 2000; Cohen et al., 1996; Kosslyn et al., 1998; Jordon et al., 2001; Richter et al., 1997; Tagaris et al., 1996; Tagaris et al., 1997; Petrides et al., 1994). All these studies involved comparing the experimental condition (deciding whether two shapes rotated were the same or different) to the control condition (deciding whether two unrotated figures were the same or different). These studies concluded that the parietal lobes are involved in the encoding and updating of spatial representations and relations in two and three dimensional mental rotation tasks. Although these functions have been primarily attributed to the superior part of the parietal lobe, it has been difficult to distinguish the functions of component regions. In addition, a number of these studies have also demonstrated that the reaction times (or response latencies) increased linearly as a function of angular disparity between the object, indicating that a rotational cognitive process was being engaged by the task (Cohen et al., 1996; Kosslyn et al., 1998; Jordon et al., 2001; Tagaris et al., 1997).

Tagaris et al., (1996) reported a linear association between superior parietal lobe (SPL) activation and errors in mental rotation performance, which suggests that greater information processing demands, were related to a concomitant increase in SPL activation. In another study, Tagaris et al. (1997) used specific parameters (percentage of

errors made, speed of performance, and rotation rate) of task performance as markers by which to identify those cortical areas that would be specifically related to the task. They found that the percentage of errors decreased, and the speed of performance increased with practice. The authors also found that the percentages of errors made were related to activation in subclusters of parietal and occipital areas of the right hemispheres and the, SPL and occipital (extrastiate) cortex bilaterally. Furthermore, as well as SPL activation these studies show weaker, but significant activation of the dorsolateral prefrontal cortex (DLPFC), the premotor cortex and the visual cortex. These areas may be engaged during active visual tracking of objects (e.g. Cohen et al., 1996; Barnes et al., 2000).

Cohen et al. (1996) identified significant bilateral activations in SPL's, the V5 complex (human motion area), the DLPFC and the premotor areas during the three-dimensional mental rotation task. The authors attributed the parietal and the V5 activations to the mental rotation processes per se, while the frontal activations were thought to represent the control of oculomotor functions required for scanning the two stimuli and the processing demands of working memory. Another important observation is that all these studies, except two (Kosslyn et al., 1998; Richter et al., 1997), tested men and women; however, they did not examine sex differences. The conclusions of these studies are difficult to interpret in the absence of analyses by sex, although all the studies demonstrated the same consistent parietal cortex activation. This will need to be taken into consideration when looking at studies that explicitly test for a sex effect.

With regard to spatial perception ability, Hannay et al., 1987) used the Xenon inhalation technique and examined performance on a version of the JLO task in a group of subjects and found activation in the temporo-occipital regions. However, this task did not strictly involve judgement of spatial position. In a more recent fMRI study, Ng et al. (2000), found robust bilateral activation of the SPL during performance on the JLO in a group of men (n=10). This finding was consistent with lesion data from 17 patients who showed substantial impairments on JLO performance after either right or left parietal damage. A more detailed analysis of the fMRI data showed a dominant role of the parietal lobe, possibly as an initial "kick-starter" of information processing during the task.

Furthermore, patients with right parietal lesions showed slightly greater impairment in their JLO performance.

Given the large sex differences in visuo-spatial functions involving mental rotation and possibly JLO, it might be expected that the neural correlates of these differences would be easily observable. A much cited study by Frederiske et al. (1999) reported that right-handed men (n=15) had larger total left inferior parietal lobule (IPL) volumes, and a non-significant trend toward leftward IPL asymmetry, compared to right handed women (n =15). Kennedy et al. (1998) also reported larger IPL, due to greater angular gyral volumes, in men compared to women, although the study made no mention of asymmetry. However, some studies have reported no sex differences in the parietal regions (Murphy et al., 1996; Good et al., 2001), whilst one study found that women had significantly more grey matter on the right parietal lobes (Nopoulos et al., 2000).

The discrepant findings could be due to factors such as absence of IPL white matter measurements in the study by Frederiske et al. (1991). In light of prior work demonstrating robust bilateral SPL activation, the finding that the left IPL is larger in males is an unexpected finding. An early study of the electrophysiological basis of sex differences in mental rotation examined event-related potentials (ERP's) of performance between 10 men and 10 women on a two-dimensional letter rotation and the PMA figures test (Desrocher et al., 1995). Although the authors found no sex differences in behavioural performance (reaction times; RT's for solving the task), shorter ERP latencies (at N1, no differences in N2, P3 or P4 components) and greater positivity of the waveforms were found in women compared to men. These authors concluded that women require more cognitive resources to perform mental rotation tasks, the ERP differences being indicative of differential strategy usage.

In a study of nineteen 8 year olds (10 boys), and 20 adults (10 males), Roberts and Bell (2000) reported that adult men had faster RT's on mental rotation than adult women, whereas boys and girls did not differ. Adult men also showed more activation (lower EEG values) in the parietal and posterior temporal regions compared to adult women,

whereas the EEG values of boys and girls did not differ in these regions. These two studies suggest some differences in the electrophysiological patterns of cortical activity between men and women during mental rotation tasks, and possibly sex by age differences indicating developmental changes that may reflect performance differences, although their precise meaning is unclear. Moreover, the findings of the latter study are puzzling in the face of prior work demonstrating robust sex differences early in childhood on mental rotation tasks (e.g. Levine et al., 1999).

Unterrainer et al. (2000) conducted a HMPO- SPECT study in a group of 13 subjects (6 men and 7 women) during performance on visuo-spatial tests (Wilde-Intelligenz- Test; similar to the paper folding task), and reported no sex differences in brain activation on the task. However, when they split the group into good and poor performers, they found a more symmetrical pattern of brain activation in frontal and parietal regions in poor performers, whereas an increased left frontal and right parietal brain activity was found for good performers.

At present there are only three studies of adult sex differences in visuo-spatial functions using fMRI. In one study, Thomsen et al. (2000) presented right-handed men (N=6) and women (N=5) with a mental rotation task based on the three dimensional figures from the Shepard and Metzler test. During the experimental condition, subjects were required to decide whether the two three dimensional figures were the same or different, and in the control condition two-dimensional vertical and horizontal bars were presented on the screen, and subjects were required to simply press left or right buttons. Thomsen et al. (2000) found that while bilateral activation of the SPL's was demonstrated for the whole sample, analysing the data by sex revealed that men showed more bilateral activation in the parietal lobe and women more activation of the right inferior gyrus. These differences were reported in the absence of sex differences on the behavioural data. A recent BOLD (blood oxygen level dependent) fMRI study (Gur et al., 2000) examined sex differences in activation on a spatial task (JLO) compared with a verbal analogies task that does not typically show sex differences. Hypothesised regions of interest analysis (ROI) were based on prior literature (in this case the authors identified the IPL and the planum

temporale; PT as of primary interest). The results demonstrated left lateralized changes for the verbal task in the IPL and PT regions in both men and women with no sex differences reported in behavioural performance. Only men showed right lateralized increase for the spatial task (JLO) in these regions as well as performing better than women at the behavioural level. Image based analysis revealed a distributed network of cortical regions activated by the tasks, which consisted of the lateral frontal, medial frontal, mid-temporal, occipito-parietal, and occipital regions. For men, the activation was more left lateralized for the verbal and more right lateralized for the spatial task, but men also showed some left activation for the spatial task. Increasing task difficulty produced a more distributed activation for the verbal task and more circumscribed activation for the spatial task. Thus, men showed more bilateral activation of these regions compared with women. Regions of the IPL have been implicated as critical for performance on complex spatial orientation and verbal analytic reasoning tasks, while the PT is an important region for perception of language stimuli (Geschwind, 1984;Geshwind and Levitsky, 1968). These regions (IPL, PT) showed significant hemispheric effects in a PET study that used the same tasks as used above (Judgement of Line Orientation and the verbal analogies task (Gur, 1983).

The results of Gur et al.'s (2000) study are of some importance as their results were consistent with those of a similar study looking at sex differences conducted by Wendt and Risberg (1994). They reported, as did Gur et al. (2000) that women showed less lateralized CBF increase in the IPL and PT than men for the spatial task, where men tend to perform better than women. Men and women showed identically left lateralized activation for the verbal analogies task, where there are no sex differences in performance. The results suggest that for regions with primary involvement in verbal and spatial processing tasks, more right lateralized activation for spatial tasks is observed in men and could relate to better performance at the behavioural level. Therefore, the regionally specific effects support the role of the temporoparietal juncture in complex verbal reasoning and spatial processing tasks (Mesulam, 1985).

Gur et al. (2000) argue that their findings support the 'bilateral advantage' hypothesis, which assumes that bilateral brain activation leads to a greater advantage across tasks, leading to the prediction that men will show bilateral brain activations for spatial tasks (confirmed by Gur et al.'s study) and women for verbal tasks. Moreover, their findings also suggest that optimal performance may require unilateral activations of primary regions (e.g. IPL and PT), and bilateral activation of associated regions. However, Gur et al.'s study does not discuss why they found that both IPL and PT were activated, and showed sex differences in lateralization, during the spatial task, given that the PT is typically ascribed to a role in language functions.

A more recent fMRI study examining the neural substrates of sex differences on the mental rotation task in men and women who did not differ in the behavioural task performance, reported activation in intraparietal sulcus, IPL and SPL, inferior temporal gyrus and premotor areas bilaterally in women, whereas men demonstrated activation in right parieto-occipital sulcus, left intraparietal sulcus and left superior lobe (Jordon et al., 2002).

Overall, the findings of these studies are difficult to reconcile, particularly in drawing conclusions about the relationship between performance and its neural correlates. Roberts and Bell (2000) reported bilateral parietal activation in males and higher scores on mental rotation, whilst Uterrainer et al (2000) reported no sex differences in brain activity, Thomsen et al. (2000) reported bilateral parietal activation in men but no differences in performance, Gur et al. (2000) reported increased right parietal and PT activations, with some bilateral activation in occipito-parietal regions during JLO, and a male advantage in performance, whilst Jordon et al. (2002) reported bilateral parietal activation in women and right parieto-occipital and left SPL activation in men, whereas their sample did not differ in performance. One possible conclusion is that, regardless of performance differences, the parietal region is 'hard-wired' for spatial processing in the male brain. When performance differences are evident, the recruitment of additional regions may reflect 'plasticity' in the neural response to information-processing demands.

1.4.3 Neural Correlates of Verbal Abilities

As discussed in the first section of this chapter, several studies have proposed that language is more strongly lateralized in men than in women (Levy, 1972; Hampson and Kimura, 1992; Kimura, 1999). Several lines of evidence support this hypothesis; firstly, men have a higher incidence of aphasia after lesions to the left hemisphere (McGlone, 1977; Inglis and Lawson, 1981). This led to the search for direct evidence in normal subjects for sex differences in the lateralization of language. The PT is an area that contributes to the phonological processing of auditory input (Binder et al., 1996) has been reported to be more asymmetric in men (Kulynych et al., 1994). Structurally, the isthmus of the corpus callosum, which contains commissural fibers connecting the posterior language areas (de Lacoste et al., 1985), is reported to be larger in women, relative to the total area of the corpus callosum (Witelson, 1989; Steinmetz et al., 1995, 1996; Jancke et al., 1997). It has been suggested that these anatomical findings are responsible for the more symmetrical representation of language in women (Witelson, 1989).

Many studies have demonstrated that the prefrontal cortex (PFC) is integral to verbal processing and executive functioning, and tests of verbal fluency are particularly sensitive to, and useful 'markers' of, prefrontal dysfunction (Lezak, 1994). Lesions to the frontal lobe have been shown to impair performance on phonological fluency, whilst damage to the temporoparietal cortex (in addition to frontal lobe damage) results in category fluency impairment (Milner and Petrides, 1984).

The past decade has focussed attention on the cerebral organization of language abilities in men and women. With regard to structural differences, a series of post mortem and structural MRI studies show that women have proportionally (to total cerebral volume) larger grey matter volumes in the DLPFC, the PT of the superior temporal gyrus (part of Wernicke's area) and the inferior frontal gyrus (IFG) (in Broca's regions) (Good et al., 2000; Harasty et al., 1997; Schlaepfer et al., 1995). Harasty et al., (1997) reported no size

differences, although Good et al. (2000) reported larger right IFG and PT regions in women only (the latter report examining 465 adult brains). A study of the cytoarchitecture of Broca's regions revealed higher cell densities in both left and right sides in female compared to male brains (Amunts et al., 1999), whilst Witelson et al. (1995) reported increased neuronal density and numbers in the female temporal cortex. However, one study has reported no sex differences in grey matter volumes in the superior temporal gyrus, DLPFC and IFG in 42 male and 42 female brains (Nopoulos et al., 2000).

Some robust sex differences are found in functional neuroimaging studies. Three studies using fMRI have demonstrated that women activated the IFG bilaterally during phonological processing (rhyme judgement) whereas men activated left IFG, and no differences were detected during orthographic (letter recognition) or semantic processing (semantic category judgement) (Pugh et al., 1996; Pugh et al., 1997; Shaywitz et al., 1995), and no sex differences were found in task performance (error rates). These studies concluded that women devote greater bilateral inferior frontal resources to phonological encoding and retrieval, the components involved in proficient verbal fluency. For example, Pugh et al. (1996) investigated component processes in reading, and reported significant sex differences in the cerebral organization of word identification processes in reading. This study was aimed at isolating the cortical networks associated with component processes in reading. The authors reported that phonological processing (processes which result in the identification of phonemic constituents of the printed message) made maximum demands on a number of frontal and temporal sites, whereas orthographic processing (processes which result in letter identification) activated the lateral extrastriate sites and lexical-semantic processing (processes which result in the successful identification of the word's meanings, rendering that information available for all higher level processing) made demands on the middle superior temporal sites. Sex differences were reported in the frontal regions. Men appeared to show greater left hemisphere activation, while women did not show the same pattern. In addition, a majority of the female subjects produced stronger bilateral activation in the IFG, whereas men did not show this pattern. In orbital gyrus, an area most strongly associated with

phonological processing; there was greater left hemisphere than right hemisphere activation reported in men.

Another study by Jaeger et al., (1998) using PET to measure cerebral blood flow (CBF) found sex differences in the IFG activated by grammatical (generation of past tense forms of verbs) and reading tasks. The researchers attempted to examine sex differences in functional cortical organization for language in general, and also looked at the possible link between any such differences and task complexity. Men and women were asked to read real and nonsense verbs and to produce past tense forms, which increases the linguistic demands of the task. The authors did not find any behavioural differences between the sexes on any of these tasks. However, they reported significant sex related differences in CBF patterns. During the past tense generation tasks, men showed left lateralized activation while women exhibited bilateral activation of the perisylvian cortex, which has previously been established to be involved in language processing. This study further confirms differences in functional laterality. During all the tasks women showed greater activation in occipital and cerebellar regions. Extrastriate occipital regions are well established as cortex, which process visual-spatial information (Miyashita, 1993). The increased activity in women suggests that they were performing more visual processing of the stimuli than men in these cortical areas. The fact that this activation is bilateral may be related to the findings of anatomical studies, which show that the splenium of the corpus callosum is larger in women than in men, suggesting that women may have more connections between posterior brain regions. Jaeger et al. (1998) also found activation in the anterior temporal lobe, which is consistent with the findings that this area is involved in grammatical processing (Witelson et al., 1995; Mazoyer et al., 1993).

Jaeger et al., (1998) found that, in their study, areas activated in the right hemisphere overlapped with areas found by Shaywitz et al., (1995) and Pugh et al., (1996) and that these areas were activated more in women compared to men during a phonological task. Specifically, activation was reported in the right IFG, anterior to the central locus. This area of activation is compatible with the findings of the previous studies, suggesting that

more phonological processing is involved in computing past tense forms from stems than simply reading them aloud (Shaywitz et al., 1996). Furthermore, the fact that Jaeger et al. (1998) found greater sex differences during the past tense tasks is consistent with the hypothesis that sex differences are more likely to emerge as the linguistic demands of a task become greater, i.e. as task complexity increases. Another PET study investigating sex differences in visual recognition of letters found minimal sex differences (Price et al., 1996).

An important point to note is that in the above studies (Shaywitz et al., 1995; Pugh et al., 1996; Jaeger et al., 1998), nonsense words were sufficient to elicit sex differences in the IFG, suggesting that semantic processing of the words had little if anything to do with sex differences in the frontal areas. Additionally, other studies have reported no significant sex differences in neural activation during verb generation from nouns (Buckner et al., 1995; Jaeger et al., 1998), stem completion of a word from its parts (Buckner et al., 1995), or when subjects are required to process semantic aspects of individual words (Shaywitz et al., 1995; Pugh et al., 1996; Frost et al., 1999).

Frost et al (1999) replicated Pugh et al.'s (1996) design with a larger sample of men (n=50) and women (n=50), and found no sex differences in brain activation during performance on a task that required judgement of the semantic categories of a spoken word. In this study, the subject was instructed to judge whether an animal, presented aurally, was both 'found in the United States ` and 'used by humans`. In another study, Buckner et al., (1998) used PET to examine performance on a word stem completion task compared with visual fixation, and verb generation compared with noun reading, and failed to find any sex differences in either behavioural performance or brain activity. The studies that have used language tasks and found no sex differences in neural activation have two common features: 1) the tasks deal with individual words; and 2) they cannot be applied to nonsense words.

Kansaku et al. (2000) argue that prior imaging studies focussed on phonological processing and not semantic processing (involved in category fluency tasks for example).

Some recent neuroimaging studies have found sex differences in the posterior language areas during passive listening to spoken narrative (Kansaku et al., 1999, 2000; Phillips et al., 2000). Kansaku et al. (1999, 2000) carried out an fMRI study on a group of men and women whilst they listened to an essay read out aloud in Japanese, and the same story played in reverse. The authors found that comparing activation in the superior and middle temporal gyri during a story with activation that occurred when the story was replayed in reverse showed left lateralized activity in men, but not in women. However, differential activation in the temporoparietal cortex was lateralized to the left in both sexes. The authors concluded that the activation in the middle temporal gyrus resulted from processing the narrative, whereas activation in the temporoparietal cortex was involved in phonological processing of word forms (Peterson et al., 1988, 1989).

From these findings the question still remained as to whether the sex differences found in the temporal gyri depended on processing global structure in the narrative, or whether the local structure of a word or words immature to form a sentence was sufficient. This point was further investigated by presenting another series of sound stimuli, designed to maintain local structure for up to 1s while disrupting the global structure in the original narrative. The results showed that with little global semantic structure, the same areas appeared to be activated in both sexes. The authors concluded that the sex difference was specific for global semantic structure (Kansaku et al., 2000). Similar findings to those of Kansaku et al. (2000) have been reported by Phillips et al. (2000). They found that the sex difference in listening to global semantic structure was evidenced for the English language and are not specific to Japanese. Therefore, from these studies it appears that the processing of the global structure of a sentence and multiple sentences produce sex differences in lateralization, whereas word tasks dealing with single word semantics elicit left dominant activity in both sexes.

With regard to verbal fluency, fMRI studies have shown robust activation of the inferior PFC, particularly, the left DLPFC and IFG (associated with the phonological loop and executive components of the task) during phonological fluency, whilst greater activation of the left temporal cortex (associated with greater access to semantic storage and

retrieval) is apparent during category fluency (Gourovitch et al., 2000; Mummery et al., 1996; Paulesu et al., 1997). As in normative studies of mental rotation, imaging studies of verbal fluency have also used male and female subjects, and not examined sex differences (Paulesu et al.'s 1997, study consisted of male participants only). In an fMRI study of a group of young subjects, Pihlajamaki et al. (2000) reported activation in the left medial temporal lobe, in the inferior frontal and retrosplenial cortices bilaterally and the left SPL during a category fluency test. Phelps et al. (1997) examined brain activation in a group of subjects (7 men, 4 women), whilst performing an overt verbal fluency task. The authors reported activation in the left IFG and anterior cingulate. Both neuroimaging and clinical studies have shown that phonological and category fluency tasks are not equivalent in terms of their neural substrates. As yet, there have been no functional neuroimaging studies of sex differences during verbal fluency tasks.

One fMRI study found no sex differences in brain activation during covert verbal fluency (subjects were required to sub-vocalise words beginning with a letter spoken to them via an intercom, with a counting task as a control condition), although this study was not specifically conducted to look for sex effects (Schlosser et al., 1998). Verbal fluency studies are difficult to carry out in the scanner. This is partly due to the difficulty in interpreting the findings, given that overt and covert verbal fluency paradigms present a number of difficulties. Firstly, although overt fluency tasks allow measurement of performance, they increase head-movement and susceptibility-related artefacts in imaging data. In addition, the continuous acoustic noise generated by the fMRI scanner may introduce potentially confounding effects on activation and make it difficult to hear subjects responses. Secondly, covert fluency, although reducing the risk of artefacts, have no objective performance measures. More recent imaging acquisition methods such as the *compressed sequence design* provide a solution for future studies. This design involves an experimental condition where subjects overtly generate words while images are not being acquired (but their performance is) beginning with a stimulus letter presented a few seconds earlier (during which images are being acquired in order to capture phonological retrieval processes). During the control condition, subjects sub-

vocally repeat a specified neutral word (e.g. "rest"). This provides us with one solution to the problem.

A recent study conducted an overt verbal fluency with easy (either T, L, B, R, S or T, C, B, P, S) versus hard letters (O, A, N, E, G or I, F, N, E, G) in young men using this compressed sequence design (Fu et al., 2002). The authors found that subjects made twice as many errors on the hard letters compared to the easy letters. Overall, the reported activation in anterior cingulate, left middle and IFG, parietal cortex and right cerebellum, consistent with areas found during covert verbal fluency. Also, the hard condition was associated with greater dorsal anterior cingulate activation compared to the easy condition.

Research supports the view that phonological production, syntactical and semantic aspects of language are represented in different specialised brain structures, so that different facets of language are served by different loci in the brain. Thus, it is not language per se that is represented in a single or a few identifiable sites, but the various subcomponents that are used in language (Posner and Raichle, 1994; Garrett, 1996). As with spatial functions, the differences in functional activation during verbal tasks occur in the absence of any sex differences in "on-line" behavioural measures, which may suggest a general effect of sex on language processing components. This suggests that it would be important for future studies to employ verbal fluency paradigms, which are known to elicit robust sex differences, as sex differences in neural activation during linguistic processing appear to be task-specific.

1.4.4 Neural Correlates of Verbal Memory

Another cognitive domain that women excel on is measures of verbal memory. Verbal memory impairments on the California Verbal Learning Test (CVLT) and the Weschler Memory Scale (WMS) are the most common neuropsychological feature following left anterior temporal lobectomy, which involves resection of large portions of the hippocampus and verbal memory declines proportionally to the degree of hippocampal

resection (Trenerry et al., 1993). Due to the fact that sex differences appear on those verbal memory tasks that appear to be disrupted by damage to the left hippocampus, sex differences in verbal memory may also be associated with the integrity of this region. Using the Logical Memory sub-test from the WMS, Trenerry et al. (1995) examined men (N = 59) and women (N = 66) who underwent right and left temporal lobectomy (TL). Women showed improvement in postoperative logical memory scores, whilst men showed a decline. Preoperative scores were positively correlated with both right and left hippocampal volumes in left TL women only, whilst sex differences or correlations were observed in the right TL group. Trenerry et al. maintain that women have better verbal memory outcomes than men following left TL and that women show greater plasticity in verbal memory function following insult to the left hippocampus. However, Berenbaum et al. (1997) found that although 30 women who underwent left anterior temporal lobectomy (ATL) performed better on the CVLT than 27 men, this was not related to extent of hippocampal resection. Women also used a semantic clustering strategy on the CVLT before and after ATL, and there was no effect of ATL on semantic clustering. Berenbaum et al. argued that sex differences in verbal memory were not due to the integrity of left hippocampus. Finally, Ragland et al. (2000) reported that women (N = 14) had better immediate recall scores on logical memory (WMS) and CVLT tasks and greater regional cerebral blood flow (rCBF using PET) bilaterally in the mid-temporal pole region. Increased CBF in the left temporal pole was associated with higher scores on the WMS in women only.

Taken together, these findings suggest some role for the temporal regions, possibly involving the hippocampus, on logical verbal memory but not on the CVLT. These findings highlight and reinforce the often task-specific nature of sex differences in brain-behaviour relationships.

1.4.5 Neural Correlates of Working Memory

As discussed earlier in this chapter, working memory is a process that allows humans and animals to maintain a limited amount of information in an active state for a brief period

of time, and to manipulate that information (Baddeley, 1992). This process is an integral part of several higher cognitive processes such as planning, decision-making, spatial navigation and strategy use. There have been no reliable sex differences reported in performance on working memory tests in the literature. Generally the most common working memory task studied in imaging studies, spatial working memory is mediated by a network of predominantly right hemisphere regions that include areas in posterior parietal, occipital and frontal cortex (Cohen et al., 1994; Smith and Jonides, 1999). The dorsal aspects of the frontal cortex (including the superior and middle frontal gyrus) may be disproportionately involved in the processing of spatial working memory, whereas the ventral aspects (including the inferior prefrontal gyrus) may be more involved in working memory for objects and faces (Goldman-Rakic, 1996; Ungerleider et al., 1998). In one study, Courtney et al. (1998) found that the superior frontal sulcus was bilaterally more active during a spatial working memory task than during a working memory task with faces. Moreover, they reported that the left inferior frontal cortex shows more sustained activity during face working memory than during spatial working memory.

Several authorities have suggested that neurons in the PFC show patterns of activity that strongly suggest their role in the temporary maintenance of information (Fuster and Alexander, 1971; Kubota and Niki, 1971). Nelson et al. (2000) investigated the neural correlates of spatial working memory in children (aged 8-11 years), using fMRI under three conditions; (1) visual condition, where children are asked to examine the location of a dot on the screen, (2) motor condition, where children were instructed to push a button that corresponded to the location of a dot presented on a screen, and (3) memory condition, where children were instructed to remember the location of a dot presented one or two trials previously. In the memory minus motor condition, activation was observed in the dorsal regions of the PFC and in the posterior parietal and anterior cingulate cortex. The same was reported for the memory minus visual conditions, except that motor cortex activation was also observed.

Few studies have examined sex differences in regional cerebral brain activation during performance on spatial or non-spatial working memory paradigms. Speck et al. (2000)

investigated sex differences in brain activation during performance on four different verbal working memory tasks that varied in task difficulty, in a group of 9 men and 8 women. Overall, they found activation of lateral PFC, the parietal cortex and the caudate in men and women. Men showed bilateral activation or right-sided dominance in these areas, whereas women exhibited activation predominantly in the left hemisphere. FMRI studies using the N-Back working memory task, have generally reported activation in the DLPFC, parietal cortex and in anterior cingulate. (Cohen et al., 1994; Braver et al., 1997; Jansma et al., 2000; Callicott et al., 1999; Smith et al., 1998; Postle et al. , 2000). Jansma et al. (2000) conducted an fMRI study using the spatial N-back task to distinguish activation during non-specific task related processes from specific workload processes in a group of healthy subjects. Load sensitive processes reflected specific working memory functions, such as temporary retention and manipulation of information, while load insensitive processes reflects supportive functions such as visual orientation, perception, encoding and response selection and execution. Activity for both these processes was found in both DLPFC and parietal cortex bilaterally, and in the anterior cingulate. Activity in the primary sensorimotor cortex showed predominantly load insensitive activity. Also, good performance was associated with a large area of load sensitive activity in anterior cingulate, and with a small area of load insensitive activity in the right parietal cortex.

In another fMRI study examining the neural correlates of the visuo-spatial N-back working memory task, Carlson et al. (1998) found that comparing the two-back condition with the zero-back condition revealed activity in a number of regions: bilateral activation in the medial frontal gyrus (MFG), superior frontal sulcus (SFS) and the intraparietal sulcus (IPS) and in IFG and, medially in the superior frontal gyrus, precentral gyrus, SPL, IPL, occipital visual association areas, anterior and posterior cingulate areas and in the insula. The authors suggest that activation in the MFG, SFS and IPS appeared to be dependent on memory load. To date, there has been no fMRI study that has investigated sex differences on the N-back working memory task.

Taken together, working memory processes for spatial material activate the right hemisphere areas. In particular the N-Back task activates the DLPFC, parietal cortices bilaterally and anterior cingulated; however, processes not directly related to the specific demands of the spatial working memory task activate co-localised areas within the frontal and parietal regions.

1.4.6 Neural Correlates to Cognitive/Behavioural Inhibition

The neural correlates of cognitive/behavioural inhibition have been conducted using modified versions of the Stroop task. PET studies have provided the first evidence for regional brain changes during the Stroop interference test, particularly within the anterior cingulate cortex (Pardo et al., 1990; Bench et al., 1993; George et al., 1994; Carter et al., 1995; Derbyshire et al., 1998). Pardo et al. (1990) conducted a PET on healthy young subjects and reported increased regional cerebral blood flow (rCBF) of the cingulate cortex during the Stroop interference subtest as compared to the colour-naming subtest. In another PET study, which used a different adaptation of the Stroop task, Bench et al. (1993) studied healthy volunteers and varied stimulus rate, practice effects, and visual stimuli. The results of the study indicated that the pattern of blood flow was dependent upon the design of the paradigm. Subjects who had practiced the task showed changes in right orbitofrontal and mid cingulate rCBF, while unpractised subjects exhibited increased right anterior cingulate rCBF. George et al. (1994) also demonstrated activation of the left mid-cingulate of a group of healthy subjects during a PET study that used modifications of the Stroop task. Carter et al. (1995) investigated facilitation and interference effects related to Stroop performance, and found increased blood flow within the anterior cingulate. A majority of these studies were limited in their spatial resolution, however, and generally considered the entire anterior cingulate as a single functional region.

In general, fMRI studies have reported activation in the anterior cingulate cortex (ACC) during the interference condition of the colour-word Stroop tasks (Gruber et al., 2002). Gruber et al. (2002) found that a subdivision of the cingulate cortex was specifically

associated with the cognitive demands present in the interference condition of the Stroop test in healthy young adults. Peterson et al. (1999) used fMRI to examine Stroop performance in healthy subjects during congruent and incongruent conditions, and concluded that, given the increased signal intensity in response to the interference condition, the findings were supportive of a parallel distributed processing model for colour-word interference within the anterior cingulate. In another study Brown et al. (1999) studied brain activation associated with overt and covert performance of the Stroop task in a group of young people. Larger BOLD signals responses were seen in the left and right anterior cingulate, the right precuneus and the left pars opercularis during the incongrous Stroop condition relative to both colour naming and word reading baselines in silent and out aloud trials.

Bush et al. (1998) and Whalen et al. (1998) conducted fMRI studies using the Counting and Emotional Counting Stroop, respectively. They reported higher signal intensity within the anterior cingulate regions during the incongruent or negative conditions compared to congruent or neutral conditions. Another study demonstrated dissociation between the degree of conflict and ACC activation. In particular, they found that though ACC activation was very extensive when the colour hue interfered with word reading performance, the level of conflict, as measured by reaction time costs, was only moderate compared to other conditions (Ruff et al., 2001). FMRI using an event-related design found activation of the anterior cingulate, insula, premotor and inferior frontal regions (Leung et al., 2000), which is consistent with a majority of studies that have used the traditional block design (Bush et al., 1998; Whalen et al., 1998; Brown et al., 1999).

Not all studies have found activation in the ACC (Mead et al., 2002), and others have suggested that the ACC activation is not specific for the interference effect. Using fMRI blocked design, Mead et al. (2002) reported activation within the left inferior precentral sulcus and the ventral premotor region, and deactivations in the rostral component of the ACC and the posterior cingulate gyrus during the incongruent colour word condition of the Stroop interference task. The authors concluded that the selective activation within the left inferior precentral sulcus is compatible with findings from previous

neuroimaging, lesion, electrophysiological, and behavioural studies and may be related to the mediation of competing articulatory demands during the interference condition. They also suggested that activation in the ACC appears to depend on a variety of methodological factors, including the degree of response conflict and response expectancies. In another fMRI study, a frontoparietal network, including structures in the lateral prefrontal cortex, the frontopolar region, the intraparietal sulcus, as well as the lateral occipitotemporal gyrus, was activated during the incongruent compared to the neutral condition of a colour-word matching Stroop task (Zysset et al., 2001). However, no activation was detected in either the right or left hemisphere of the anterior cingulate cortex.

In addition to looking at the neural correlates of the interference conditions of the Stroop task, several studies have investigated neural activity of negative priming. The negative priming paradigm requires participants to respond to a target stimulus, which has previously been ignored as a distracter. The resulting delay in reaction time is termed the negative priming effect. Steel et al. (2001) investigated the areas of cortical activation associated with Stroop interference, Stroop facilitation and Stroop negative priming tasks. The significant areas of activation within the negative priming task included the IPL, left temporal lobe and frontal lobes. Consistent with previous reports (Carter et al., 1995, 1997; Pardo et al., 1990; Taylor et al., 1994) they also found activation of the cingulate gyrus (bilaterally) within both the Stroop interference and Stroop facilitation tasks.

Overall, the results of these studies implicate the role of the ACC in performance on Stroop tests and a more distributed pattern of activation on negative priming tests. However, no study has investigated the neural correlates of cognitive inhibition using a numerical forward backward task in either men or women.

1.4.7 Gonadal Hormones and Neuroimaging

Behavioural studies in humans (men and women) and in animal studies provide evidence suggesting that gonadal hormones such as estrogen (E) and testosterone (T) may modulate neuronal activity, and as a result affect behaviour, mood and cognition (McEwen, Fink et al., Summer and Fink, 1995). Several brain-imaging studies have examined the role of gonadal hormones, specifically concentrating on the role of E, in cognition. For example, Veltman et al. (2000) investigated brain activation during performance of a rhyme decision task in 8 young women, during the early follicular (low E and progesterone) and midluteal (high E and progesterone) phases of the menstrual cycle. The authors reported no differences in the pattern of brain activity between the two phases of the menstrual cycle. However, during both phases, they found extensive activation in left superior parietal, motor and prefrontal cortices and bilateral cerebellar, striatal and extrastriatal cortices.

In an fMRI study examining the neural correlates of a word stem completion task, a mental rotation, and a simple motor task, Dietrich et al. (2001) tested 6 men and 6 women. Women were scanned twice, once during the low E (menses) phase and then again during the high E (ovulation) phase of the menstrual cycle. The results showed no differences in brain activation between men and women on any of the tasks when women were on the low E phase of the menstrual cycle; however, a higher overall level of cerebral hemodynamic response during the high E phase of the cycle in women was reported during the word completion and mental rotation tasks, whereas the hemodynaminc effects during the motor task were less pronounced.

Berman et al. (1997) conducted a PET study in young women during three pharmacologically controlled hormone conditions 1) ovarian suppression induced by the gonadotropins-releasing hormone agonist (Lupron), (2) Lupron plus E treatment and (3) Lupron plus progesterone replacement in the span of 4-5 months. They measured regional cerebral blood flow (rCBF) during performance on the Wisconsin card sorting test (WCST), an executive functioning task known to activate PFC (and an associated cortical network including IPL and inferolateral temporal gyrus) and a sensorimotor control task (no-delay matching to sample). During treatment with Lupron alone (virtual

absence of neurogonadal hormones), the results demonstrated a diminished activation of the areas reported to be activated by the WCST and no rCBF in the PFC, in the absence of any change in behavioural performance. However, in the conditions where E or progesterone was added to the lupron treatment, a normalization of the rCBF activation pattern with an increased activation of the parietal and temporal regions and return of the dorsolateral PFC activation was reported. Another PET study conducted in older women (aged 55 and over) on estrogen replacement therapy (ERT; with or with or progesterone) compared to matched sample of untreated women, measured rCBF during performance under three conditions: rest and verbal and figural memory (Resnick et al., 1998). The authors reported significant differences in activation between the two groups (ERT users versus non users) in the right parahippocampal gyrus, right precuneus, right frontal regions and left hypothalamus during the verbal memory task. Significant interactions were reported for right parahippocampal gyrus, inferior parietal regions, and for left visual association and anterior thalamic regions for the figural memory tasks. The ERT group performed better than the non-users on the figural and verbal memory tasks. In a similar study, Maki and Resnick (2000) found that longitudinal rCBF changes over two years in a group of ERT users, compared to non users, during performance on rest an verbal and figural recognition memory task was more pronounced in the hippocampus, parahippocampal gyrus and temporal lobe. The authors concluded that these regions form memory circuits that are sensitive to preclinical Alzheimer's disease.

Shaywitz et al. (1999) measured brain activation in a group of postmenopausal women (n= 46) twice, once when taking E treatment (for 21 days) and again when given placebo (with a 14 day wash out period), during performance on verbal and non-verbal working memory tasks. They found that E treatment increased activation in the IPL during storage of verbal material and deactivation of the IPL during storage of non-verbal material. Increased E related activation was also observed in the right superior frontal gyrus during retrieval tasks, coupled with greater left hemisphere activation during encoding. They reported that E did not affect actual performance on the verbal and nonverbal tasks.

Taken together, neuroimaging studies that have examined the role of gonadal hormones in relation to the menstrual cycle have shown that E may play a role in brain function. Hormone treatment studies illustrate the importance of E in relation to brain activity during performance on verbal memory tasks and the WCST.

1.5 Neurohormonal Relationships to Neurocognitive Performance

1.5.1 Hormones and Neural Development

One of the ways in which researchers have attempted to explain why cognitive differences on certain spatial and verbal tasks are observed in men and women has been to examine the relationship of gonadal hormones to cognitive behaviour (See Linn and Petersen, 1985; Reinisch et al., 1991; Williams and Meck, 1991; Hampson and Kimura, 1988; Silverman et al., 1999). Studies investigating the effects of hormones on sexual differentiation of the brain and behaviour have been difficult to conduct on humans, due to the moral and ethical implications of these kinds of experiments. However, animal experiments have made it possible to study these effects due to the convenience with which it is possible to manipulate their hormonal environment. For example, Williams et al. (1990) showed that prenatal reversal of androgen exposure in male and female rats reversed sex typical maze learning ability.

Much of the information on the role of gonadal hormones on human development has been obtained from studies of naturally occurring fluctuations in hormone levels, as well as from situations where hormone levels have been manipulated either naturally or experimentally in both men and women of all ages. There is evidence that these hormonal influences may extend to problem-solving abilities (Williams et al., 1990) and that cognitive patterns may vary with phases of the menstrual cycle in normally cycling women (Hampson, 1990; Rosenberg and Park, 2002) and with seasonal variations in androgens in men (Wieneiski and Nelson, 2000; Kimura and Hampson, 1994).

1.5.1.1 Sexual Differentiation- Basic Mechanisms

Before proceeding to sections that will discuss the relationship of hormones to cognitive abilities in general, and to neurocognitive sex differences, it is of primary importance to understand the neurodevelopmental and physiological processes through which gonadal hormones act in sexual differentiation, because complications that occur at any stage of these processes can lead to possible hormonal conditions after birth, during adolescence and adulthood.

In the early stages of development, male and female foetuses appear undifferentiated genetically, and it is assumed that in the absence of masculinising factors, the developmental default sex is female. Some authorities have argued that this may be a simplistic model as there is some evidence that suggests that the presence of ovarian may also be needed for "active" feminisation (Collaer and Hines, 1995; Collaer et al., 2002). However, evidence for this is still weak and in its early stages. In a genetic male (XY), the testis determining factor (TDF) gene (also known as SRY) causes the undifferentiated gonads to develop into testes, which as a result produce testosterone (T) and the Mullerian Regression Factor (MRF). The role of the MRF is to regress the Mullerian ducts (female), T virilizes the Wollfian ducts (male), which then become the internal male reproductive system. T acting under the enzyme 5-alpha reductase, converts to dihydrotestosterone (DHT), which forms the appearance of the external male genitalia, whilst conversion of T to estrogen (E) via the enzyme aromatase contributes to masculinisation of neural substrates (in rodents, maybe to a lesser extent in primates, Halpern, 1992; Kimura, 1999; Becker, Breedlove and Crews, 1993). Because a large amount of T is converted to E (or estradiol) in the brain, when conclusions are drawn about androgenic influences on behaviours, it is often difficult to differentiate between the effects of T (in fact that is 5-alpha reduced T) versus the effects of aromatised T (estradiol) within the brain. Also, T can convert to DHT within the brain, particularly in white matter tissue (Kimura, 1999; Becker et al., 1993).

The function of the gonads (ovaries and testes) is of importance in regulating hormone levels. However, the brain structures most directly involved in regulating hormone levels in both sexes are the hypothalamus and the pituitary gland. The hypothalamus is thought to act as a "relay station", integrating hormonal stimuli, which travel through the blood stream, and neural stimuli from many other parts of the brain. The hypothalamus is also involved in the production of "neurohormones", or releasing factors, which pass through the pituitary portal vessels into the anterior pituitary, stimulating the synthesis and release of pituitary gonadotrophic hormones, including LH and FSH. These pituitary hormones are carried in the blood to the gonads, where they regulate the production and secretion of gonadal or steroid hormones; primarily T in males and primarily E and progesterone (PROG) in females. In turn, these steroid hormones are released into the blood and registered in the hypothalamus as part of the complex feedback mechanism contributing to hormonal regulation (Dyrenfurth et al.,1974; Speroff and Vande Wiele, 1971; Becker et al., 1993; Johnson and Everitt, 1988).

It is thought that there are two control systems for pituitary gonadotropins in the hypothalamus; one component exerts cyclic control, and the second exerts "tonic" or continual control (Whalen, 1968). Tonic regulation exists in both males and females, and is responsible for maintaining the basal level of gonadotropin secretion through a negative feedback mechanism. Cyclic control has been thought to occur only in women, and the cyclic mechanism depends on both the positive and negative feedback systems to regulate the occurrence of ovulation. Androgen secreted by the male foetus during a critical period of development (prenatal) in humans causes this sex difference in hypothalamic function (Whalen, 1968).

In general, hormones have two major influences on brain and behaviour. These are known as 'organizational' and 'activational', and vary in their permanence and in the developmental time period during which they occur. Brain development is very much dependent on the quantity and type of steroid hormone available during brain formation; this type of effect is called organisational because of the early effect on the way neural substrates assume specific and relatively permanent functions (Goy and McEwen, 1980;

Berenbaum et al., 1995; Collaer and Hines, 1995). The organisational effect is thought to occur because hormones have a prime role in directing basic processes of neural development; for example, they play an important role in deciding cell fate, cell connectivity and which neurotransmitters they use (Arnold and Gorski, 1984; Summer and Fink, 1998). Gonadal hormones such as T and its metabolites, dihydrotestosterone and estradiol are known to influence the organization of the human brain during critical periods in development before or just after birth, and can permanently alter a human being's propensity to engage in many sexually dimorphic behaviours (Kimura and Hampson, 1994). Studies in rodents, primates and other mammals, have shown that the hypothalamus, hippocampus, the preoptic-septal region and the limbic system are important target areas for gonadal hormones actions (e.g. McEwen, 1992, 2002; Collaer and Hines, 1995). There are several ways in which researchers have studied the relationship of organisational effects of sex hormones to cognitive functioning. These include examining the relationships between umbilical and amniotic hormone samples and cognitive performance (Finegan et al. 1992; Grimshaw et al. 1995; Jacklin et al. 1988). Individuals with gender identity disorders (E.G. CAH, Turners Syndrome, Androgen Insensitivity Syndrome) also provide information on the role of early hormone environment on cognitive performance. Finally, somatic markers, such as 2nd to 4th finger length ratio, has also been found to be strongly related to testosterone and estrogen ratio (Lutchmayer et al. in press).

Conversely, activational influences are temporary and fluctuate as hormone levels rise and fall. These influences are known to occur during puberty and thereafter in humans. For example, in adulthood, gonadal hormones continue to activate certain neural circuits and their consequent functions. The different ways in which researchers examine activational effects of hormones in relation to cognitive performance are: to examine exogenous hormones on cognitive performance (e.g. hormone replacement therapy in older men and women, gender reassignment, administration of hormones to individuals with gender identity disorders), endogenous levels of cognitive performance (e.g. during different phases of the menstrual cycle). It is important to note that when examining the relationship of gonadal hormones to cognitive performance in men and women, testing

the same individual at different times of the day represents an appropriate measure of activational effects of gonadal hormones on cognitive performance.

The goal of this thesis is not to discuss the molecular details of gonadal hormone action. Therefore, let it suffice to summarise the following: I) 'organizational' effects refer to gonadal steroids binding to their receptors (e.g. androgen or E receptors) in neuronal cells (forming a steroid-receptor complex) and subsequent binding of this complex to DNA, where it regulates gene transcription, thereby exerting powerful influences on the development and differentiation of neuronal cellular morphology and functioning, and II) activational effects refer to the same processes with the addition that steroid-receptor complexes regulate gene transcription and affect intracellular reactions, such as changing cell membrane potentials, producing short term (relative to the long lasting organizational effects) inhibitory or excitatory outcomes.

Investigators have established androgen and E receptor expression in brain regions of both humans and animals associated with higher cognitive functioning. These areas include the human temporal cortex, and sub-cortical structures such as the hippocampus (e.g. Bixo et al., 1995; Puy et al., 1995; Beyenburg et al., 2000; McEwen, 1992).

Since experimental manipulations of hormone levels cannot be conducted in humans due to ethical and moral considerations, our knowledge of hormonal effects on human cognitive sex differences derives from investigations of normative, between subject and within subject variations in endogenous levels of gonadal hormones and the examinations of exogenous levels of hormones on cognitive functioning. The following sections will discuss, the role of prenatal (organisational), endogenous (activational) and exogenous (hormone treatment) levels of gonadal hormones on cognitive functioning.

1.5.2 Prenatal Hormone Influences on Neurocognitive Performance

Examination of normative differences between individuals has demonstrated a number of interesting associations between gonadal hormone levels and sexually dimorphic

cognitive performance. Research investigating umbilical and amniotic hormone samples have found inconsistent information for an influence of early T levels and improved cognitive performance. Finegan et al. (1992) found no association between amniotic T levels (2nd trimester) and cognitive functions in boys (language comprehension, language expression, block-building, figure disembedding, counting, verbal memory and IQ), but found that in girls, prenatal T levels showed a curvilinear (inverted U-shaped) relation to language comprehension and classification abilities and that prenatal T levels were inversely related to girls' scores on tasks involving counting and numbers. Also, girls with high average block building scores had lower prenatal T levels compared to those with low average block building scores (both groups aged 4 years). In a follow up study of these children at 7 years, Grimshaw et al. (1995) found a positive association between prenatal T levels and speed of mental rotation in girls and the opposite trend in boys. Also, in another study, Grimshaw, Bryden and Finegan (1995) found that higher levels of prenatal T in girls was related to stronger right- handedness scores and greater left hemisphere language representation as assessed by the fuse dichotic-listening task. Boys with higher levels of prenatal T demonstrated a right hemisphere bias for word affect recognition (also presented dichotically).

A similar study, conducted by Jacklin et al. (1988) reported relationships between early hormone levels and cognitive abilities in normal children. They explored the associations between neonatal cord blood levels of hormones and cognitive abilities at 6 ½ years. The results demonstrated that cord blood levels were inversely related to girls' spatial ability, but no relations were observed for boys. The interesting points to note about these studies is that findings from both these studies suggest that T may have different relations with the cognitive abilities of girls and boys. Secondly, results from both Finegan et al. (1992) and Jacklin et al. (1988) studies indicate that, for cases in which the relationship between early androgen exposure and cognitive abilities in girls are observed, higher levels of T are associated with lower test scores.

Parallel to these findings, one study investigated the influence of salivary levels of T on spatial ability (two-dimensional spatial task) in prepubertal children (Ostatnikova et al,

1996). They compared two groups of children: gifted boys and girls (N=81) from experimental classes of elementary school (mean age 6 years) and a control group of normal boys and girls (N=70) from elementary school (mean age 7.5 years). The results showed significantly lower T levels in gifted children (boys and girls) compared to the control group. The gifted children performed better on the spatial reasoning tasks and in this sample of children, T correlated negatively with cognitive performance.

Overall, the results from these studies suggest a small influence of prenatal T levels (suggestive of an organizational effect) on neurocognitive performance in both boys and girls, but the results are not consistent with the predictions. It appears that lower levels of T were related to better performance on cognitive tasks. Some researchers argue (e.g. Kimura, 1999) that the findings of these studies are inconclusive because the assay techniques did not differentiate between foetal and maternal hormone sources, because of unclear critical periods for hormonal differentiation in humans, and insensitivity of the cognitive tests to normative sex differences.

The influence of prenatal gonadal hormones on neurocognitive performance has also been studied in individuals exposed to unusual hormone environments early in development (until corrective hormonal therapy). The main sample groups studied in this area are women exposed to the synthetic E diethylstilbestrol (DES), women with congenital adrenal hyperplasia (CAH) a genetic disorder causing increased androgen production during early development due to 21-hydroxylase deficiency, or men with idiopathic hypogondotropic hypogonadism (IHH), where men are exposed to low levels of androgens during early development. In animals, prenatal exposure to androgens or estrogens enhances the development of male-typical behaviour (masculinizes) and impairs development of female typical behaviour (defeminizes) (Hines and Sandberg, 1996). Synthetic estrogens, such as DES, have been found to stimulate neural E receptors and treatment with DES produces similar masculizing and defeminizing effects (Hines, Alsum et al., 1987; Hines and Goy, 1985, Williams, Barnet et al., 1990; Williams and Meck, 1991).

Several studies have examined the cognitive abilities of individuals exposed prenatally to the synthetic E diethylstilbestrol (DES) (Hines and Sandberg, 1996; Smith and Hines, 2000). DES studies typically use larger samples, powerful to detect effects, and are notable in finding no effect of E on two or three-dimensional mental rotation, verbal fluency, JLO, map learning, water level test, Raven's SPM and hidden figures test (Hines and Sandberg, 1996; Hines and Shipley, 1984). Hines and Sandberg (1996) found that there were no differences between DES-exposed women and their unexposed sisters in cognitive abilities at which women excel on average (verbal fluency, perceptual speed and accuracy and associative memory), for abilities that men excel on average (visuo-spatial abilities), or for abilities that do not show sex differences. Also, they found that the time of prenatal exposure to DES, related to visuo-spatial performance, with later exposure associated with better performance. In another study, Hines and Shipley (1984) reported that DES-exposed women and their unexposed sisters performed similarly on a spatial relations task requiring mental rotation of two-dimensional shapes and on a verbal fluency task.

In contrast to these findings, Resnick et al. (1986) demonstrated that women with CAH demonstrated enhanced visuo-spatial abilities (usually favouring men) compared to their unaffected female relatives. Another study assessed hand preference and language lateralization in women exposed to DES prenatally and in their unexposed sisters (Smith and Hines, 2000). The authors found that the DES exposed women were more likely to be left handed for writing. However, there was no difference between the groups on a dichotic listening measure of language lateralization. Also, they found that exposure to hormones early in gestation was related to left-handedness, whereas exposure in late gestation was associated with reduced left ear (right hemisphere) scores on the verbal dichotic task.

These findings suggest that although prenatal androgens may influence some aspects of sexually dimorphic cognitive functioning, it does not so via conversion to E. In the studies described so far, any differences in neurocognitive functioning observed are less likely to be attributable to socialisation factors, for example, CAH girls are reared gender

typically (most studies also use their unaffected sisters as a control group to partly to rule out parental socialisation influences).

Several studies have found that CAH-girls show improved performance on block-building, Spatial Relations test, two dimensional mental rotation task, and one study demonstrated improved performance on a three dimensional mental rotation task in CAH girls (reviewed in Collaer and Hines, 1995; Hines, 2000; individual studies; Hampson et al, 1998; Resnick et al., 1986; see also Hines et al., 2003). No differences have been reported between exposed and non-exposed controls in verbal fluency or perceptual speed. One study reported that CAH boys and girls showed greater shifts towards left handedness, higher performance IQ's compared to verbal IQ's (on the WAIS-R) and no differences in dichotic listening task (Kelso et al., 2000). Nonetheless, many CAH studies fail to find differences in spatial and non spatial functions, while the pattern of abilities in CAH males is unclear (Hines, 2000). One consistent observation in CAH girls is their increased male-typical play behaviours and interests (such as rough and tumble play), a factor, which may be a proximal bio-social variable for enhanced spatial functions (Berenbaum, 1999; Berenbaum and Hines, 1992; Berenbaum and Snyder, 1995; Iijima et al., 2001).

Thus, CAH women may seek out experiences conducive to the encouragement of male typical spatial skills. CAH studies also do not have sample sizes large enough to detect effects with any degree of confidence (N's around 6-18); larger samples are difficult to acquire as CAH occurs in only 1 in 14,000 live births.

Studies with regard to ovarian influences on cognitive abilities have examined groups of women with Turner's syndrome (TS; characterised by a missing X chromosome leading to physical abnormalities, and notably, primary gonadal failure). In general, the phenotype of TS is characterised by a cognitive profile, which assumes normal verbal skills, impaired visuo-spatial and visual perceptual skills and impaired nonverbal more than verbal memory. One study found that Turner's women, compared to their unaffected sisters and female cousins, performed poorly on a domain of female-favouring tasks,

including verbal fluency, object-location memory, perceptual speed and digit symbol recall (Collaer et al., 2002), compared to a domain of sex-neutral tasks (Vocabulary and Computation). These differences remained after covariance for differing spatial activities and sex-related childhood interests. In this study, it remains unclear whether any hormonal effect is attributable to E or progesterone because of primary ovarian failure in the condition. In another study E treatment in a group of young girls with TS (aged 7-9) was compared to placebo treated group with TS and a control group. The findings showed improved verbal and nonverbal memory (digit span, Children's word list immediate and delayed recall) in the E treated group and also reported that their performance was similar to the control group (Ross et al., 2000). In a similar study, E and placebo treated girls (aged 10-12) were compared to aged matched female controls on tests of nonverbal and motor functioning. Again, E had a positive effect on nonverbal processing speed and speeded motor performance, slower performance on these tasks is found in E-deficient girls with TS (Ross et al., 1998).

With regard to studies of men, Hier and Crowley (1982) reported that men with IHH showed decreased visuo-spatial abilities compared to matched controls, and to men whose hypogonadal state began later in life. In another study, Imperato-McGinley et al (1991) compared performance of individuals with complete androgen insensitivity (AI; genetic males who are unresponsive to androgens), thus having a female phenotype (develop female genitals and are usually raised as girls despite normal or high levels of T) to controls from the same geographical area on the Spanish version of the WAIS. They found that the control men were superior to women on block design, picture completion and object assembly, and were better than the AI subjects on all five spatial subtests (block design, picture completion and object assembly, digit symbol, picture arrangement), whereas women were superior to AI subjects on all tasks except for the object assembly test. This was also found when female controls were compared to their AI sisters.

These studies demonstrate the important role of androgens in cognitive performance (especially in spatial tasks) in individuals with low T who tend to perform poorly on

these tasks compared to control samples. Furthermore, it is unclear whether this pattern of findings is due to prenatal or postnatal hormone effects, or the fact that these individuals were identified and raised as girls. Therefore, caution should be taken when understanding and interpreting these results in the context of hormonal effects on cognition.

1.5.3 Endogenous/Activational Gonadal Hormones and Neurocognitive Performance

Circulating hormone levels also vary within individuals as a function of a number of factors, including pubertal onset and menstrual cycle phase. During puberty gonadal hormones levels rise dramatically, under the control of the hypothalamus, triggering sexual and physical maturation as well as influencing cognitive performance. Hassler (1991) studied boys and girls over a 7-year period (children entered the study at age's 9-14 years). The results demonstrated that early maturing boys (defined by breaking of voice) and late maturing girls (defined by onset of menstruation) performed better than their same sex peers on mental rotation and the hidden figures test. Hassler (1991) examined salivary T and E, and found that T levels for boys predicted performance on the hidden figures test in year 5 (about age 10) and mental rotation in year 6 (about age 11), whilst there were no association for girls. When these children were followed up as adults there were no associations between hormones assayed via blood samples and cognitive performance. Davidson and Susman (2001) found positive associations between T and E (assessed at baseline, 6 months and 1 year later) and spatial test scores (mental rotation and block design) at all sessions in boys and at the 1-year stage in girls (aged 9-14 years), whereas Liben et al (2000) found no associations between T and E, administered to adolescents with delayed puberty, and spatial scores (Spatial Relations tests, RFT, WLT and PFT) over a 21-month period (tested every 3 months) in a randomised trial alternating between hormones and placebo.

Waber in 1976 postulated that, regardless of sex, early maturing adolescents would perform better on verbal functions than on spatial functions, whereas late maturing adolescents would show the opposite pattern (based on a hormonally influenced slower maturation which causes the male brain to be more right hemisphere orientated). One study supporting Waber's hypothesis, reported that later self-reported pubertal onset was related to improved performance on a box-folding task in women (Meurling et al., 2000). Also, in an earlier study, Herbst and Peterson (1980) found that late maturing adolescents performed better than their early maturing peers on the embedded figures test.

However, some later reports have discounted this theory proposed by Waber, and found that age at puberty has limited validity in terms of explaining the biological basis of cognitive sex differences (Newcombe and Dubas, 1987; Signorella and Jamison, 1986)

Extraneous factors need to be taken into account when interpreting these findings, including the variances in assay methodologies, but also the possibility that earlier measurements may reflect variations in the timing of puberty rather than absolute hormone levels at maturity (assessed at the later stages in studies). Neither can the effect of pubertal increases in hormone levels on sex-typical activities and interests (as well as the appearance of sexual characteristics on diverging gender role formation) be excluded as a facilitatory variable in the development of spatial functions.

Natural variations in T levels on within sex cognitive differences have been another area of research, which has also provided inconsistencies in the literature. One point of focus in research concerns the issue of quadratic influences of T and E on cognitive performance (or the curvilinearity hypothesis), that is, a proposed inverted U-shaped relationship between E (aromatised T) and spatial functions such that too low or too high levels move the individual from an optimal peak (Nyborg, 1994).

To date, various attempts have been made to investigate the relationship of T to spatial abilities in men; however, the associations between plasma and salivary levels of T and spatial abilities have shown conflicting results. Some studies have reported positive

linear relationship (Christiansen, 1993; Christiansen and Knussman, 1987; Janowsky et al., 1994; Silverman et al., 1999), negative associations (Gouchie and Kimura, 1991; Kimura and Hampson, 1994), null relationships (McKeever et al., 1987; McKeever and Deyo, 1990) and curvilinear relationship between endogenous T and visuo-spatial ability (Moffat and Hampson, 1996; Shute et al., 1983). In one study Christiansen and Knussmann (1987) investigated the relationship of sex hormones to cognitive functioning in 117 young men. They collected blood and saliva samples to determine the serum concentrations of T, 5α-dihydrotestosterone (DHT), and the level of free T (TS) in the saliva. Performance on five spatial tasks and 6 verbal ipsative test scores, which reflected intra-individual variance in the performance of these tasks, independent of the person's general level of achievement, were obtained. The results revealed that serum T levels and to a lesser extent DHT and TS showed a significant positive correlation with measures of spatial ability and field dependence-independence, and a significant negative correlation with measures of verbal production.

In another study, salivary measures of T levels were taken in fifty-nine men at times of the day when T was expected to be highest and lowest (Silverman et al, 1999). Relationships were evaluated for mean T levels across the two sessions and hormone level changes between sessions with performance on the three-dimensional mental rotation test, and the anagrams and the digit symbol tests were used as control tasks. The mental rotation scores showed a significant positive relationship with mean T levels, but not with changes in T levels, and there was no relationship between mean T levels and the control tasks. Gouchie and Kimura (1991) reported a nonlinear relationship between salivary levels of T and spatial ability. They used a larger sample of participants and made use of non-spatial as well as spatial tasks. They examined the cognitive performance of 42 men and 46 women, grouped according to whether the subjects had relatively high or low salivary T concentrations. The results suggested that men with lower T performed better than other groups on measures of spatial/mathematical ability, which usually favour men. Women with high T scored higher than low-T women on these same measures. Thus, optimal levels of T in men results in poorer performance and in women better performance on spatial task performance.

A study by Neave and Menaged (1999) provided further information on the relationship of T to cognitive functioning in sexual orientation by providing evidence of both within-and-between- sex differences in cognition, and indicates that these differences may be partly accounted for by the activational effects of free T. They investigated the performance of both heterosexual and homosexual men and women on four sexually dimorphic cognitive tasks and found significant sex and orientation effects on one spatial (mental rotation) and one verbal (verbal associations) task. They also reported significant relationships between salivary levels of T and performance on both spatial tasks, but not the verbal tasks.

The relationships between gonadotropins and visuo-spatial abilities in men and women have also been examined (Gordon and Lee, 1986). The authors found that that higher levels of FSH were associated with poorer performance on visuo-spatial tests (spatial orientation and point localization) in men and women (only for the spatial orientation test), and FSH as well as LH was positively related to word fluency. Also, no associations with verbal functions across these studies were reported.

With regard to the curvilinearity hypothesis, there has been no study that has provided robust evidence of the U-shaped curve. Although cited as supportive, Moffat and Hampson (1995) investigated the relationship between salivary levels of T and performance on visuo-spatial (spatial visualisation and spatial orientation) and verbal cognitive tests (controlled associations test and the control oral word association test), in left and right-handed men and women. To control for circadian variation in T, they collected salivary samples for subjects randomly allocated to one of two testing sessions, (0815 h or 1015 h). Among the sample of right-handed subjects, they found salivary T to be negatively correlated with spatial performance in men and positively correlated with a measure of spatial visualisation in women. The researchers reported that across the observed range of T, there was a curvilinear relationship between spatial cognition and T in right handed, but not in left handed subjects. Also, they found a significant difference in accuracy measures on the spatial task among right-handed people tested in early vs.

late sessions, which was in accordance with the expected diurnal change in circulating T. Moffat and Hampson (1999) concluded that intermediate levels of T were associated with better spatial functioning. However, they raised the possibility that hand preference may be a factor that moderates the observed relationship. The findings of Shute et al. (1983) are similar, although they also called the associations observed curvilinear. A major limitation in this study was that there was no distinction made between the effects of T and other androgens, since the antibody used in the radioimmunoassay was assumed to bind to other androgens biochemically similar to T. Also, they failed to determine the relationship between androgens and non-spatial tests.

It is unclear why the above studies report divergent results, although all have measured T levels at different times in the day (morning levels are higher than any other time of the day) and different test administration procedures have been used (such as time allowed for task completion, even though in all cases sex sensitive tests are used). However, some support for the curvilinear hypothesis was provided by the observation that men perform better on mental rotation, paper folding and hidden figures when tested in the spring season than men tested during the autumn season (when circulating T levels are higher; Kimura and Hampson, 1994; Kimura, 1996), whilst men tested in the late morning score higher on mental rotation than men tested during the early morning (Moffat and Hampson, 1996). Sanders et al. (2002) also found improvement on mental rotation scores in men during afternoon testing (and no differences in block design), and an even larger improvement when tested later in the afternoon. Mens also showed improved verbal fluency from the morning to the afternoon. These authors also found more improvements in a right ear advantage on verbal dichotic listening during the afternoon than in the morning, primarily due to increased right ear accuracy in men and women.

Wisiniewski and Nelson (2000) measured functional cerebral lateralization in a group of men and women in the spring and fall. Measures of free T were obtained to determine the associations between seasonal variability in lateralization and seasonal fluctuations in T exposure. The authors found that men and women tested in the spring showed exaggerated patterns of asymmetry compared to subjects tested in the fall. Lower T

concentrations were found in the spring compared to the fall in women, but not in men. However, they found no direct association between T and lateralisation for either sex at either season.

In general the above studies have found that lower T levels are associated with improved spatial performance; consistent with the curvilinearity hypothesis, and that possibly, left hemisphere functioning is impaired with higher T levels. Though, overall, it seems that the relationship of T to spatial ability remains unresolved and there is still conflicting findings in this area. Future studies may also need to take into account the role of gonadotropins as well as T when examining the relationship to spatial ability.

The relationship of endogenous T to cognition has not been restricted to spatial abilities. Circulating/endogenous levels of hormones have also been studied in relation to a range of cognitive tasks in men and women. Kampen and Sherwin (1996) investigated the relationship of circulating levels of plasma E2 and free T to performance on visual memory, visuo-spatial ability, verbal memory and attention tasks in a sample of young healthy men. Subjects' mood at the time of testing and their sociodemographics were recorded. The results suggest that higher plasma E2 was associated with significantly better performance on two measures of immediate visual memory: visual paired associates and visual reproduction. These findings were reported in the absence of any differences in mood, demographic variables, or attention between the high and low E groups. Due to the absence of an effect of T on the cognitive performance of young men, it appears that circulating levels of T had no relationship to the abilities examined. However, subjects exhibited a limited range of T levels (half of the total range of normal values for their particular assay), and this restricted range may have precluded detection of significant relationships between performance on the cognitive tasks and T levels.

Janowsky et al. (1998) examined the relationship between E and T to sex differences in cognitive performance. Men outperformed women on spatial ability (block design, card rotation) and dart throwing. They found no sex differences in verbal and non-verbal memory, verbal fluency, or fine motor performance. Hormone levels (E and T) were

related to performance on tasks that show sex differences as well as those that do not. E and not T was related to block design in women but not men, and women with higher E performed better overall than women with low E. No relationship between hormone levels and card rotation was reported. Also, positive relationships were found between both E and T and dart throwing performance.

These studies demonstrate that the relationship between gonadal hormones and cognitive performance is not consistent. From these studies E appears to relate to cognitive performance in women, whereas T does not robustly relate to performance on spatial ability in men.

Studies of endogenous levels of E and T in men and women also have provided some important information on the role of declining levels of hormones on cognitive performance. A recent study looking at endogenous levels of T and E on cognition in older men (aged between 59-89) found that high levels of total and bioavailable E were related to poor scores on the Blessed information memory concentration test (BIMC) and the mini-mental state examination. Men with higher levels of bioavailable T had better scores on the BIMC and the Bushke – field selective reminding test (Barret-Conneret al., 1999). Morely et al., (1997) found that declines in T levels in older men were associated with declines in both visual and spatial memory and verbal fluency. In another study, Drake et al. (2000) examined the relationship between circulating levels of gonadal hormones (E and T) and cognitive performance in a group of healthy elderly women. They found that high E levels were associated with better delayed verbal memory and retrieval, whereas low levels were associated with better immediate and delayed visual memory, and levels of T were positively associated to verbal fluency. Wolf and Kirschbaum (2002) examined the relationship between endogenous E and T and cognition (verbal memory, spatial memory, verbal fluency, mental rotation, susceptibility to interference) in older men (mean age 69) and women (mean age 68). They demonstrated that in women high E and T levels were associated with better verbal memory (paired associates) and E not T was associated with less susceptibility to

interference (Stroop). In men, they reported a negative relationship between T and verbal fluency.

A majority of these studies have examined serum E levels alone and do not take into account the concentrations available to the brain. In one study, Yaffe et al. (2000) measured non-protein bound and bioavailable E and total and non-protein bound T in relation to cognitive performance (mini mental status examination; MMSE) in women (baseline and 6 years later). They found that females with high serum concentrations of non-protein bound and bioavailable E, but not T, were less likely to develop cognitive impairment than women with low concentrations. In another study, Yaffe et al. (2002) found no association between total T and cognitive performance (MMSE, Trails B, Digit symbol); however, men with high bioavailable T had better scores on all the tests. Also, total E levels were related to worse scores on all the tests, although bioavailable E was not related with cognitive performance and sex hormone binding globulin (SHBG) was negatively associated with all cognitive tests.

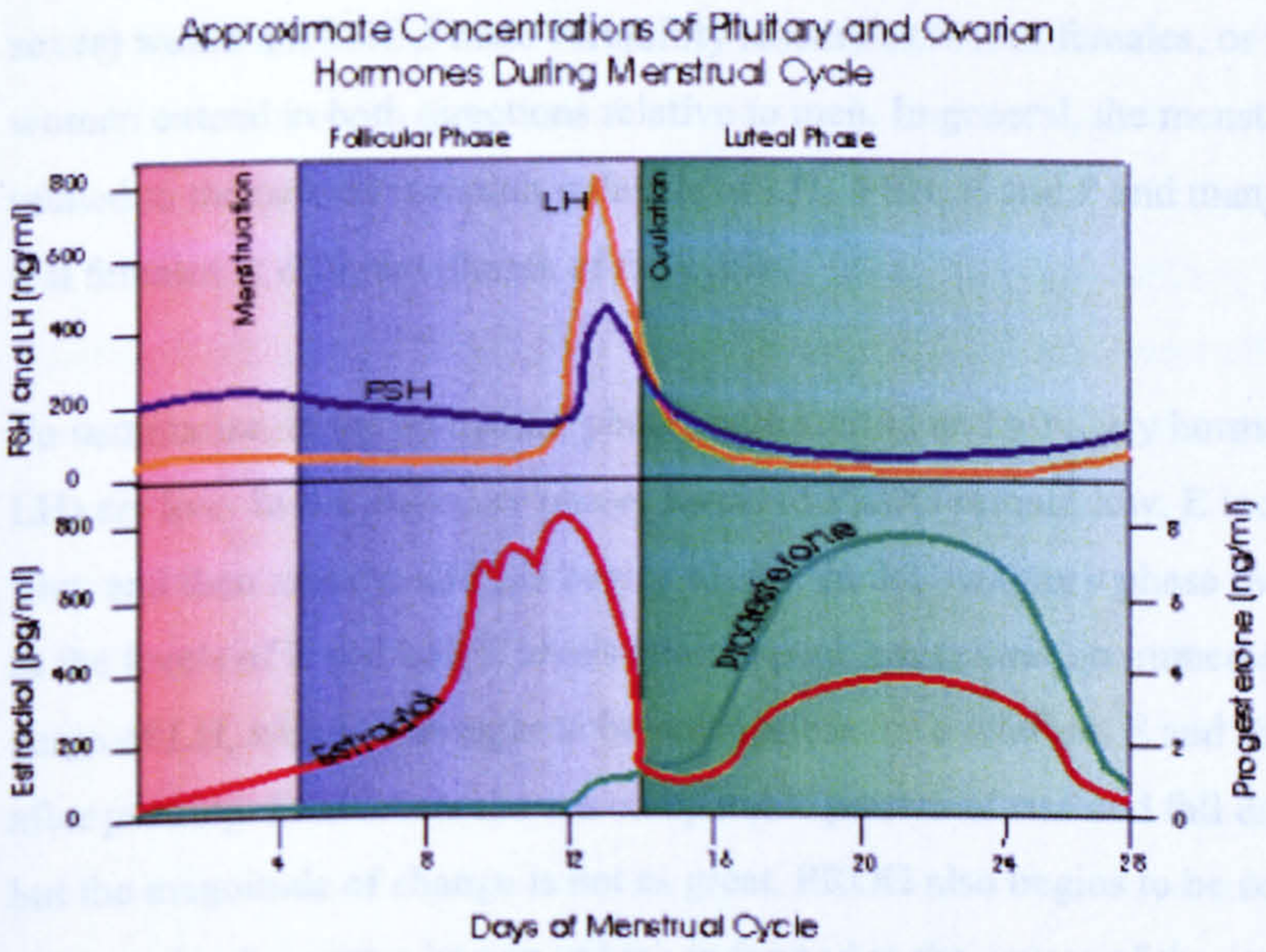
Overall, the findings of the relationship of declining gonadal hormones to cognitive abilities in older men and women are inconsistent. Sex hormones appear to have differential relationships to cognitive abilities in men and women. It seems difficult to make sense of the pattern of findings because some studies have measured T and E, whereas others have measured free and bioavailable E and T. Also, studies differ in the cognitive measures used, and the time of testing as well as the number of times hormone measures were taken. These factors, as well as the time of menopause, need to be taken into account when examining the relationship of declining basal/endogenous gonadal hormones to cognitive performance.

1.5.3.1 The Menstrual Cycle

The menstrual cycle consists of two main phases that are defined by levels of several hormones (see Figure 1.2). The first fifteen days of the menstrual cycle make up the *follicular* phase, during which FSH stimulates an ovarian follicle to develop and secrete

the hormones estradiol and estrone (collectively E). The increased levels of E causes reconstruction and proliferation of the uterine lining and stimulates the pituitary to produce LH, which reaches its peak at mid-cycle (about day 15). The LH peak causes the mature follicle to release the ovum, which then travels towards the uterus via the fallopian tube. LH also signals the development of the corpus luteum, a secretory organ developed from the original site of the ovum.

Figure 1.2 Graph showing concentrations of pituitary and ovarian hormones during the menstrual cycle



The second half of the menstrual cycle is the *luteal* phase, during which E and PROG are secreted by the corpus luteum to prepare the endometrium for implantation should fertilisation occur. If fertilisation or implantation does not occur, secretion of E and PROG ceases, followed by degeneration and expulsion of the endometrium during menstruation (when E and PROG are at their lowest, mid-luteal phase is when E and PROG are expressed at the highest levels). At this point the pituitary is stimulated again by the hypothalamus to release FSH and the cycle begins again.

Menstrual cycle changes may contribute to sex-related differences in cognitive functioning in two conceptually distinct ways. First, if the menstrual cycle adds variation to females' performance, it would lead to a sex-related difference in variability itself. Secondly, if the variations are predominantly in one direction, and significantly affect a large enough proportion of women, they could contribute to the sex-related differences in average levels of cognitive performance. For example, if the performance of females on a verbal fluency task was high at a certain point of the cycle, and spatial ability was low at a certain point, then the likelihood that some subgroups of women would be in those phases at any given moment could influence group differences between the sexes (Englander-Golden et al., 1977; Klaiber et al., 1974). This latter hypothesised effect (i.e. prevalent unidirectional variation contributing to cognitive differences between the sexes) would not hold if male variability resembles that of females, or if the variations in women extend in both directions relative to men. In general, the menstrual cycle is related to the natural variation in levels of LH, FSH, E and P and many of the studies test females at different phases of the cycle.

To summarise, in the *menstrual* phase, both steroid and pituitary hormones levels (FSH, LH) are low. In the *follicular* phase, levels of PROG remain low, E increases slowly at first, and then rapidly, and LH begins to rise. In the *ovulatory* phase there is rapid change in the levels of E and LH. E levels attain a peak concentration immediately prior to a surge of LH, which is thought to be responsible for ovulation. E and then LH descend after peaking. FSH levels show a comparable pattern of rise and fall during this phase, but the magnitude of change is not as great. PROG also begins to be secreted in increased amounts by the corpus luteum, which is formed in the course of the ovulation process. During the luteal phase, both E and PROG rise and remain at high levels, while LH and FSH slowly decrease. In the *premenstrual* phase, which consists of the days prior to the onset of menstruation, E and PROG levels are declining, and FSH is on the increase to stimulate the ovaries to begin a new cycle (Speroff and Vande Wiele, 1971).

In addition to these hormonal variations, physiological changes occur during the menstrual cycle. These include: changes in blood chemistry, temperature, basal metabolism, adrenal and thyroid functioning, sodium and water retention, autonomic nervous system functioning, etc. Some of these systemic changes are thought to be related to changes in the gonadal hormones (e.g., the higher basal body temperature during the second half of the cycle is considered to be the result of higher PROG output), but many changes are of unknown etiology (Southam and Gonzaga, 1965).

1.5.3.2 Cognition Across the Menstrual Cycle

In general, studies on the menstrual cycle have found that during the luteal phase (when E levels are high) women perform poorer on tests of mental rotation, spatial relations (of the PMA), the EFT and the RFT, and better on verbal fluency and fine motor tasks than during the menstrual phase (low E and PROG phase) (e.g. Hampson and Kimura, 1998; Hampson, 1990; Philips and Silverman 1997; McCormick and Tellion, 2001; Rosenberg and Park, 2002). Philips and Sherwin (1992) found that significantly lower visual memory (delayed recall) scores were associated with the menstrual phase compared to the luteal phase. The decrease in visual memory was significantly correlated with plasma PROG in the luteal phase. Also, scores on the paragraph recall test were negatively correlated with free T levels, whereas, paired associate learning was positively correlated with E levels in the luteal phase. Also, Silverman and Phillips (1993) reported significant increases in mental rotation scores during the menstrual phase of the cycle when E is at its lowest. In another study, Rosenberg and Park (2002) tested women (n=8) with regular menstrual cycles and a group of women on non-tricyclic birth control pills four times during one cycle. They found that periods of high E levels were associated with improved verbal working memory, as measured by the verbal span score. Moreover, McCormick and Tellion demonstrated that the cyclical differences in cognition were not due to variations in perceived stress, perceived success, mood and CORT levels (stress hormone).

One study in rhesus monkeys found improved performance during a positional spatial memory test during the menstrual rather than pre-ovulatory (in which E levels surge) phase (Lacreuse et al., 2001), whereas Postma et al. (1999) reported better object location memory in women tested during the pre-ovulatory rather than the menstrual phase. In another study, Sanders and Wenmoth (1998) reported greater right ear advantages for a verbal dichotic listening task during the midluteal phase, and greater left ear advantage for a music dichotic listening task during menses. Low left ear (right hemisphere) scores for both tasks were observed from menstrual to midluteal transition, suggesting more bilateral processing during the period of elevated E and PROG (See also Hausmann and Gunturkun, 2000). However, not all studies have replicated these differences (Epting and Overman, 1998; Gordon et al., 1986; Gordon and Lee, 1995).

Furthermore, contrary to some of the previously mentioned studies, one study reported that women were better on JLO during the high E rather than the low E phases of their menstrual cycles (Chiarello et al., 1989).

The inconsistencies in menstrual cycle studies could be due partly to the absence of accurate hormonal measurements in order to verify cycle phase (and to correlate hormone levels with cognitive performance). Epting and Overman (1998) reported that only 11 of 62 studies on cognition and menstrual cycle effects conducted hormone measurements. Furthermore, these studies cannot differentiate between the effects of E compared to PROG, although researchers have assumed that E is the responsible hormone (c.f. Hausmann and Gunturkun, 2000). Two robust studies using serum radioimmunoassay (RIA) have confirmed poorer performance in women on mental rotations during the luteal phase (Hausman et al., 2000; Maki et al., 2002) although one has not (Epting and Overman, 1988). Maki et al. (2002) also reported higher semantic fluency during the luteal phase. Both of the positive studies also reported that E levels had negative associations with the mental rotation test (Maki et al., also reporting a positive correlation with verbal fluency) and no associations with PROG levels. Hausmann et al. (2000) also reported a positive influence of T levels on mental rotation performance.

In summary, the available evidence from menstrual cycle studies suggests that both E and T are able to modulate sexually dimorphic cognitive performance over the menstrual cycle (primarily poorer performance is reported on mental rotations during high E levels), and possibly also cerebral asymmetries. However, findings are not always consistent.

There is limited literature on the role of PROG on cognitive functioning. Some menstrual cycle studies take measures of PROG to determine correct cycle phase, however, the relationship between PROG and cognition is not well established. Previous studies investigating the effects of oral PROG administration on attention performance in women pointed to putative sedative effects of PROG at high doses. A study carried out by Gron et al, (1997) examined whether dosages of PROG that influence sleep produce sedative hangover effects on the following morning. The researchers assessed the effects of a single oral dose of 300mg micronized PROG administered in the evening, on cognitive performance in healthy young males on the following morning using a placebo-controlled double-blind cross-over design. There was greater variability in bioavailable PROG following intake. In terms of cognition, PROG produced no consistent effects on performance on an attention task. Certain metabolites of progesterone are reported to be potent and selective positive allosteric modulators of the γ-aminobutyric acid type A ($GABA_A$) receptor. Administration of progesterone can demonstrate behavioural effects that include, anxiolysis, sedation and analgesia (Lambert et al., 2003). More studies need to be conducted in order to gain a better understanding of the relationship of PROG to cognitive abilities.

1.5.4 Stress Hormone – Cortisol and Cognitive Functioning

The main body of evidence suggests that the hypothalamic-pituitary-adrenal (HPA) axis dysfunction (activated in response to both physical and psychological stress) or a state of hypercortisolaemia can be correlated with cognitive deficits specific to the temporal lobe declarative memory system (see Jameison and Dinan, 2001 for review).

The stress hormone cortisol (CORT) has been suggested to affect cognitive functioning and changes in hippocampal morphology in rats (Sapolsky et al., 1985) and monkeys (Roberts et al., 1987). For example, long-term exposure to CORT has been found to cause pyramidal cell death in the hippocampus, accompanied by severe declarative memory impairments (McEwen et al., 1992). In humans, elevated CORT levels have been found to be associated with decreased hippocampal volumes (Starkman et al., 1992) and impairments in explicit, declarative memory (Wolkowitz, 1990; Wolkowitz et al., 1990), However, not all studies have reported this (Domes et al., 2002).

One study found that increases in CORT levels over time were associated with decreases in delayed paragraph recall scores in elderly women, but not in men (Seeman et al., 1997). In another study, sex differences in age-related changes to the HPA axis were reported (Seeman et al, 2001). This group found that salivary "free' CORT responses to a cognitive challenge (the paired associate task from the Weschler Memory Scale-Revised, digit symbol test, Stroop test, delayed recall of the paired associates) in younger (aged 22-26) and older (67-88) men and women revealed an age-by-gender interaction; younger men had greater CORT response to the cognitive challenge as compared with younger women, while the reverse was true for the older adults (i.e. older women were found to exhibit greater responses compared to the older men).

In another study, Domes et al (2002) found that endogenously stimulated CORT levels (using the Trier Social Stress Test) had no effect on declarative memory performance (priming free recall task) in a group of middle aged women. In fact increased levels of CORT were related to better performance on the memory task compared to lower levels. Carlson and Sherwin (1999) took measures of CORT and dehydroepiandrosterone-sulfate (DHEAS) in an elderly group of men, female E users and female non-E users and tested them on a neuropsychological battery comprising tests of verbal and visual memory, attention, verbal fluency and semantic memory at baseline and after 18 months. They found that men had higher DHEAS levels than both groups of women, and the subjects with lower CORT levels performed better than those with higher levels on tests

of declarative memory. Also, men and women taking E treatment had higher digit span scores compared to women not taking E at both testing times. The authors also found that higher CORT levels in elderly men and women are associated with poorer explicit memory functioning.

A series of studies conducted by Newcomer et al. (1994; 1999) found that treatment of a healthy group of people with glucocorticoids, had no effect on tasks designed to measure attention, whereas others have suggested that there is a selective attention impairment in cases of excess levels of glucocorticooids (Kopell et al., 1970; Wolkowitz et al., 1990). One study using EEG found that acute administration of CORT to healthy volunteers decreased the amplitude of the averaged evoked potential to attended stimuli (Kopell et al., 1970). This suggests an interference with the ability to attend selectively to target stimuli or impairment in filtering out irrelevant stimuli.

Overall, these studies demonstrate that higher levels of CORT appear to have detrimental effects on memory, especially declarative memory performance. However, the one study that found higher endogenous levels of CORT to relate to better memory performance underscores the need for more research in this area.

1.5.5 Gonadal Hormones and Cognitive Inhibition

As previously mentioned in section chapter 1, men are hypothesised to perform better than women at inhibiting their responses to obvious stimuli, in favour of less obvious stimuli (Broverman et al., 1968). This sex difference in cognitive inhibition has been attributed to the differences in the relationship between adrenergic activating and the cholinergic inhibitory neural processes, which are also sensitive to androgens and E.

Based on animal studies, Broverman et al. (1968) postulated that superior performance of females on perceptual motor tasks is related to the activating effects of E. However, in men, androgens also seem to increase activation, although to a lesser extent than E. The authors suggested that the cognitive activation-inhibition differences between sexes in

both animals and humans may be primarily due to sex differences in E. A later study conducted by Broverman et al. (1981) investigated performance of women on an automatization and inhibition task. The group found that high levels of E in women during the midcycle phase of the menstrual cycle was related to better performance on the automatized tasks, and poorer performance on perceptual restructuring tasks, compared to performance on these cognitive tasks in the postovulatory phase of the cycle when PROG is thought to counteract the action of E. There have been no studies to date that have examined the relationship between gonadal hormones and cognitive inhibition in healthy men and women.

1.5.6 Exogenous Hormones and Cognition

A number of situations provide opportunities for studying exogenous hormone treatment on hormone-behaviour relationships, such as: medical conditions where endocrine dysfunctions require hormonal treatment; hormone treatment to individuals seeking sex-reassignment (transsexuals), and volunteers for male contraceptive pill trials.

1.5.6.1 Exogenous Hormones and Cognition in Women

Levels of gonadal hormones such as E and T have been found to decline with age. As a result, this decline has been related to the acceleration of the age effects on cognition (Halbreich, 1995). For example, menopause in women occurs around the age of 50 and is marked by the cessation of ovulation and a dramatic decline in the production of ovarian hormones (e.g. E and PROG). During this time, women often report short-term memory loss and forgetfulness (Hackman and Galbraith, 1976). In general, hormone replacement therapy (HRT) can be prescribed as a treatment for menopausal symptoms and consists of either oral or transdermal E and a progestin, or E alone in cases where a female has had a full hysterectomy.

The hippocampus has long been implicated as the primary site for the actions of E and androgens on cognition. Animal studies have shown that declarative (explicit) memory

(e.g. delayed non match to sample test, radial arm maze) is considered the cognitive function most vulnerable to menopausal loss of E. E treatment to ovariectotmised rats results in increased hippocampal neuronal excitability (Terasawa and Timiras, 1968), alteration of hippocampal dendritic spine density (Woolley et al., 1997), and blockage of this effect with E replacement therapy (ERT; Gould et al., 1990). There are few preclinical behavioural correlates to these findings. For example, Luine (1994) and Luine and Rodriguez (1994) demonstrated a decline in performance on the eight-arm of the radial arm maze after ovariectcomy in rats in two separate studies.

In humans, support for E related hippocampal morphological change is indirect. All assumptions of a relationship between E and the hippocampus come from studies of hippocampal-dependent cognitive processes, such as explicit memory or free recall.

Androgen effects on memory may be mediated through several mechanisms. The hippocampus, which also underlies spatial abilities as well as declarative memory, contains both T receptors and E receptors (Roof and Havens, 1992; Luine, 1994). Therefore, T may have direct effects on the hippocampus through the androgen receptor, as well as indirect effects from aromatization to E interacting with estradiol receptors (Naftolin et al., 1975).

There are two types of E receptors, ERα and ERβ, and both have been found in the rat hippocampus. Recent in-vivo E binding studies suggest that E is likely to be involved in cognition and neuroprotection in the hippocampus and the basal forebrain (Shughrue et al., 2000; Shughrue and Merchenthaler, 2000). Behavioural effects of ERα knockout mice also suggest that E has effects on learning and memory, although the relative importance of ERα and ERβ receptors is yet to be established (Rissman et al., 1999).

Recent neurophysiological studies have suggested that the prefrontal cortex (PFC) may be susceptible to modulation by E. Many authorities have argued that the PFC is responsible for mediating a number of cognitive processes that contribute to memory function, particularly, working memory (Duff and Hampson, 2000; Keenan et al., 2001).

Duff and Hampson (2000) tested groups of postmenopausal women taking either (1) E (2) E and Progestin concurrently or (3) not taking any HRT. They found that women taking E performed significantly better than the other groups on a verbal and spatial task, both of which had a working memory component; however, they did not differ from the nonusers on the control tasks (simple passive recall). The authors concluded that E is active within the PFC and is capable of influencing functions dependent on this region. Also, these findings raise the possibility that E may play a role in maintaining certain frontal lobe functions in women.

Keenan et al. (2001) found that women not receiving HRT were relatively impaired on cognitive tasks subserved by the frontal lobes (they were impaired in correctly recognising words previously learned and distinguishing them from items not on the list, made more perservative errors, and they performed worse on the N-back task of working memory). The authors suggest that hippocampally mediated cognitive decline may be secondary to executive dysfunction. They conclude that the PFC is important for working memory and that E enhances performance on working memory tasks. Fedor-Freyberg (1997), found no effect of HRT on memory measures, but reported significantly better performance on frontally mediated visual search, reaction time, and object sorting after two months of HRT in 21 menopausal women. Also Schmidt et al. (1996) found differences between 70 treated and 140 untreated menopausal women in compartmentalization and visuo-spatial skills after correction for age, education, blood pressure and multiple comparisons, but no differences in memory performance were reported between the groups of E and non-E users. Keenan et al. (2001) argue that in many studies of ERT and cognitive functioning, memory is treated holistically and researchers have not considered the diverse cognitive processes involved in the efficient encoding, storage and retrieval of information. Brain regions beyond the hippocampus are assumed to subserve these processes. For example, the frontal lobes are necessary for choosing and implementing encoding strategies that organize the input to, and output from, the hippocampus. They also provide the monitoring necessary for successful retrieval (Moskovitch, 1994). Learning and memory are enhanced by frontally mediated processes that fall into the category of 'executive functioning', which consists of

cognitive processes that encompass working memory, directed attention, response inhibition, dual task coordination, cognitive set switching and behavioural monitoring.

A number of studies have investigated the effects of HRT on cognitive functioning in postmenopausal and elderly women using different cognitive measures of executive functioning, learning and memory, especially verbal memory, which has been suggested to be more sensitive to the effects of HRT. Not all studies have found support for the role of E in prefrontal functioning. Duka et al. (2000) studied the effects of 3-week transdermal ERT or placebo in a group of healthy elderly women who had not taken any ERT in the past. They measured memory and frontal lobe function (inhibition and planning) and visuo-spatial abilities (mental rotation) before and after treatment. They found that ERT improved memory and visuo-spatial abilities, but had no beneficial effect on frontal lobe functions.

Overall, these studies show that HRT has beneficial effects on verbal, spatial and executive functioning tasks, though there is conflicting data on the beneficial effect of E in prefrontal functioning. Although some studies show support for a modulating effect of E on the PFC, others do not support this. Future studies should disentangle the various processes involved in working memory (encoding, storage and retrieval) and relate performance on these cognitive processes to E.

A number of cross-sectional studies of community dwelling postmenopausal women have found that HRT users performed better than nonusers on short-term recall of verbal information, but not figural information (Hackman and Galbraith, 1976; Kampen and Sherwin, 1994; Robinson et al., 1994; Carlson and Sherwin, 1998; Jacobs et al., 1998). However, there is evidence that HRT use may improve the retention of some types of figural memory (Resnick et al., 1997; Resnick et al., 1998).

A selective effect of E replacement on verbal memory has also been found in prospective double-blind placebo-controlled studies of surgically menopausal women (Sherwin, 1988; Philips and Sherwin, 1992). In these studies, subjects received a postoperative

injection of either E or placebo, and were later tested on a number of cognitive measures. The researchers found that the scores on the immediate and delayed recall of paired-associates remained the same pre- to post-operatively in the E group, however, they decreased significantly in the placebo group.

Another study implicating the role of E in memory comes from females who were infertile due to the presence of a uterine myoma (Sherwin and Tulandi, 1996). In this study, patients underwent a 12-week treatment program designed to suppress ovarian hormone production. This was followed by 8 weeks of either E or placebo replacement treatment or placebo. The authors found that during the 12 weeks of hormone suppression, females' scores on a number of tests of verbal memory were reduced, as were E plasma levels. However, after 8 weeks of E or placebo treatment, there was an increase in plasma levels in the E group, as well as an improvement on scores on the verbal memory tests, and this was not observed in the placebo group.

In a randomised double blind study investigating the effects of a two week transdermal E treatment or placebo on memory performance in a group of healthy elderly women, Wolf et al. (1999) found no differences between the groups on tests of verbal, semantic or spatial memory tests (including mental rotation) and the Stroop test. However, within the treatment group, women with higher levels of E performed better after treatment on a verbal memory test (delayed recall of the paired associate test), compared to women who reached lower E levels. Kimura (1995) found that women receiving ERT outperformed women not receiving such therapy on verbal fluency, perceptual speed, spatial awareness, motor control and articulation.

In one study Binder et al. (2001) administered either placebo or conjugated E plus trimonthly progestin to a group of elderly postmenopausal women (aged 75 and older) and tested them on a large cognitive battery including tests of executive functioning, verbal fluency, Weschler Paired Associate Learning, Cancellation Random Letter and Random Form Tests. After 9 months of HRT treatment they found no significant group differences for any of the cognitive performance measures. File et al. (2002) tested the

effects of 10 years of E implants on attention, memory and frontal lobe function in healthy women who had undergone a surgical menopause compared to women who had never received HRT. They found that the long term E implants did not show any cognitive benefits. They found that E implants related to impaired functioning on some tasks (rule reversal, long-term episodic memory) compared to non-HRT users.

Smith et al. (2001) investigated cognitive domains improved or preserved by long-term HRT in a group of healthy postmenopausal women either treated with long term HRT since menopause, or who had never been treated with HRT. The HRT group performed better on the Weschler Memory Scale visual reproduction (delayed recall) and the digit vigilance test (attention). Carlson and Sherwin (2000) examined the relationship between E, free T and cognitive functioning in elderly men, women who use E and women who do not use E and tested them twice (baseline and 18 month). They found that women on E treatment and men had higher forward digit span scores compared to women who were not using E at both test sessions, and women on E had higher backward digit span scores compared to women not on E. Both groups of women performed better than men on a verbal fluency test.

Overall, these studies of the effects of HRT on cognitive functioning demonstrate inconsistent findings. The majority of studies show that there is some improvement on aspects of verbal memory and attention in HRT users and surgically menopausal women on E replacement, whereas some studies show improvements of figural memory (Resnick et al., 1997; Resnick et al., 1998). One study with infertile women showed improvements in verbal memory after E treatment (increased levels of E). In addition, some studies have shown improved performance on verbal fluency (Kimura, 1995; Carlson and Sherwin, 2000). However, the few studies that have examined the long term effects of HRT on cognitive functioning (Binder et al., 2001; File et al., 2002) did not find improvements in cognitive functioning with HRT, although one study did (Smith et al., 2001). All these studies contribute to our understanding of the role of HRT on cognitive functioning; however, the studies all use different assay techniques, different tests which

assess cognitive functions such as verbal memory, attention, time of testing varied across studies and different types and dosages of HRT were used.

Future studies need to control for these factors, and include control samples that are matched for age and IQ. Furthermore, researchers should examine the long-term effects of E replacement on cognitive functioning.

Epidemiological studies have reported that women who choose to take HRT may be younger or have higher levels of education and socio-economic class than non- users: "the healthy user bias" (Barret-Conner, 1998; Matthews et al., 1999). Thus, it has been suggested that this may explain the higher incidence of positive findings in epidemiological studies compared with experimental studies (Hogervorst et al, 2000). Few studies have matched HRT users and non-users for age, IQ and education and socio-economic class. Maki et al. (2001) examined the effects of HRT on memory and other cognitive abilities in healthy females receiving oral or transdermal ERT and in healthy matched women who have never received any HRT. Women taking E performed better on measures of verbal learning and memory (encoding and retrieval) compared to the control women, but no differences were observed on any of the other cognitive tests. Verghese et al. (2000) in a small group of elderly surgically menopausal women found that present (duration of use not specified) and past users (use for 3 years) of E had better episodic and semantic memory compared to non-users; however, the groups did not differ on measures of attention.

Kampen and Sherwin (1994) matched HRT users with non-users for time since the menopause and found that HRT users had better episodic memory (immediate and delayed paragraph recall) than non-users; however, the subjects were taking different forms of HRT, and the duration of HRT was not specified. Fluck et al. (2002) used a pair matching technique, whereby pairs of women were matched on age, years since the menopause, IQ, years of secondary education, occupation and anxiety and depression scores. Women that had taken tibolone (HRT) for 10 years had better semantic memory compared to the controls, but the groups did not differ in episodic memory and HRT

users performed worse on a sustained attention and a planning task, tests that are associated with frontal lobe functioning. Similar findings were reported by Barrett-Connor and Kritz-Silverstein (1993) who controlled for age and education. They conducted a naturalistic study of 800 post-menopausal women and found no differences in performance on tests of verbal or visual memory among women with diverse histories of hormone replacement. Never used, past users and current users all performed equally well. However, those women who had used HRT for 20 years had better semantic memory, but did not differ in tests of episodic memory or attention.

In summary, these epidemiological studies that have examined the effects of HRT on cognitive functioning directly implicate E as the active agent, and lead to draw the conclusion that the benefits of HRT may be limited to short-term memory for verbal material. However, factors such as the different methodologies, duration and type of HRT may be possible reasons for inconsistencies in the findings.

With regard to tasks favouring women, a series of studies has shown a beneficial effect of E treatment (compared to non E users) on verbal fluency (Carlson and Sherwin, 1998; Grodstein et al., 2000), logical memory, digit ordering, and manual speed tasks (Carlson and Sherwin, 1998; Duff and Hampson, 2000; Kimura and Hampson, 1994) in healthy elderly women. The activational effect of T on selective aspects of object location memory was examined by Postma et al. (2000). The authors found that a single dose of exogenous T in healthy young women improved performance in the delayed recall condition, in which subjects have to both reconstruct the precise locations and to link the different objects to the correct places compared to the placebo group.

1.5.6.2 Exogenous Hormones and Cognition in Men

Like E in women, serum levels of total T, bioavailable T (T that is not bound to sex hormone binding globulin), and free T in men decrease with age. This decrease is associated with decreased muscle mass and strength, osteoporosis, and reduced sexual

activity, as well as changes in cognition. T replacement therapy has been reported to have beneficial effects on all the aforementioned outcomes. With regard to cognition, age related declines in T appear to affect spatial memory, although studies have not always reported consistent findings (Cherrier et al., 2001). In a double-blind, placebo-controlled study of older, hypogonadal men, Sih et al. (1997) administered biweekly injections of 200mg T cypionate. They found improvements in grip strength; however, there were no significant changes on measures of memory. Similarly, Wolf et al (2000) administered a single T (250 mg T enanthate) or a placebo injection in a group of healthy elderly men, and found that after one week, T injections blocked the practice effect in performance on a verbal fluency task, but had no effect on spatial or verbal memory. In contrast, Janowsky et al. (2000) examined the relationships between sex steroids (T and E) and working memory in both younger and older subjects. T supplementation (150 mg T enanthate administered weekly for 4 weeks) enhanced working memory performance in older men and related positively to working memory performance in younger men (Janowsky et al, 2000).

An earlier study carried out by Janowsky and colleagues (1994) reported that older men given exogenous T performed better on a visuo-spatial task than did their matched placebo controls, although performance on a visual memory task did not differ between groups (Janowsky et al. 1994). Cherrier et al (2001) administered either 100 mg T enanthate or placebo for 6 weeks to a group of healthy elderly men in a randomised double-blind design. They found increases in levels of T and E (because of aromatization of T to E), and they observed significant improvements in spatial memory (route recall), spatial ability (block design) and verbal memory compared to baseline and placebo groups, but had no effect on verbal fluency. The authors concluded that it remains unclear whether these improvements in cognition were a result of increased T or E levels or both.

Gordon et al (1986) demonstrated that injection of lutenizing hormone releasing hormone (LHRH) prevented improvement on the mental rotation test across three testing sessions

(although improvement was observed in a placebo condition) in men and women, whilst T treatment had no effect in men.

In studies administering supraphysiological levels of T, O'Connor et al. (2001) reported that T treatment in eugonadal men taking part in a contraceptive trial was associated with deficits in block design and improvements in verbal fluency at week 4 of an 8-week trial (in a single blind placebo controlled study). Alexander et al. (1998) found no effect of T levels on male- favouring spatial tests in eugonadal males receiving T as part of a male contraceptive trial. Alexander and colleagues did however report that hypogonadal men (who show failure in the production of T) showed improvement in verbal fluency following T treatment.

To summarise, studies examining the effects of T treatment on cognitive functioning have demonstrated inconsistent findings. Some studies, but not all (Gordon et al., 1986; Sih et al. 1997; Wolf et al., 2000) show that T treatment in men has some beneficial effects of tests of visuo-spatial ability, working memory and spatial and verbal memory. One study showed that T treatment blocked the practice effect on performance on a verbal fluency task in men (Wolf et al., 2000), whereas improved performance on this test was observed in males receiving T as part of a male contraceptive trial. Overall, the inconsistent findings may be a result of the different testing protocols used. For example, studies differ in the dosage and the length of time T was administered. Also, studies use different tests to assess cognitive functions. Furthermore, it is possible that these beneficial effects of T may be a result of the conversion of T to E through aromatase. Future studies should control for these factors and also examine the long-term effects of T treatment in men.

1.5.7 Gender-Reassignment and Cognition

Male-to-female transsexuals (administered anti-androgens and synthetic E) have been reported to show cross-sex shifts in sex typical cognitive performance, namely poorer spatial ability (mental rotations and hidden figures test), and improvements in verbal

fluency. Conversely, female-to-male transsexuals (undergoing E suppression and androgen treatment) were reported to show the reverse shift; that is, improvements in spatial ability and poorer verbal fluency (e.g. Van Goozen et al., 1994, 1995). Slabbekoorn et al. (1999) replicated the findings for spatial functions but not for verbal fluency. However, Miles et al., (1998) found no difference between male-to-female transsexuals undergoing E treatment and those awaiting treatment in mental rotation or verbal fluency, but they did report higher scores on verbal memory (PAL test) in the treatment group.

To summarise, studies on exogenous gonadal hormone treatment suggest an improvement in verbal memory as well as verbal fluency during E treatment and some improvements in visuo-spatial functions and spatial memory, tasks known to be sensitive to sex differences. However, the T-treatment studies also point to a positive effect of T on verbal fluency scores in men. The supraphysiological doses of hormones used in the protocols of these studies needs to be considered when forming conclusions about normative processes (for example, such large doses exceed the capacity of binding factors, such as sex hormone binding globulin, of hormones in the blood), as do the non-normative nature of the conditions examined.

Chapter 2: Hormones, Neurocognition, and Symptomatology in Schizophrenia

2.1 Sex Differences in Clinical Features in Schizophrenia

Schizophrenia is a debilitating disorder, which affects approximately 1 percent of the population worldwide (Eaton et al., 1988; Gold and Weinberger, 1995). The disorder is equally prevalent in men and women. The two sexes differ, however, in the onset and course of illness (Angermeyer and Kuhn, 1988; Hafner et al, 1994). Onset has been reported to be earlier in men than in women. Despite a small number of reports to the contrary (e.g. Castle and Murray, 1993), it is generally accepted as a robust finding in the literature, that males are younger than females at onset of schizophrenia and at first hospital admission for schizophrenia (Goldstein et al., 1995; Lewine, 1988; Eaton, 1985). Although an earlier age of onset (AOO) in men has been reported by several studies, few have taken account of the parameters that might confound this observation. For example diagnostic criteria include or exclude different groups of patients from the diagnosis. Some researchers have set strict criteria for diagnosing patients with schizophrenia, which included an onset of illness before age 40 years, and a family history of schizophrenia and illness duration of at least 6 months (Farone et al. 1972). Others, however, have set a more liberal criteria in that a diagnosis is made after just 2 weeks of illness, and removing the criteria for AOO and family history (Spitzer et al. 1978). These differences in diagnosis are important when considering sex differences in schizophrenia, as different sets of diagnostic criteria, when applied to the same group of men and women with a psychotic disorder, diagnose different proportions of men and women as having schizophrenia (Castle, 2000). Several factors have been related to an earlier AOO, these include: a family history of schizophrenia (Alda et al., 1996), obstetric complications (Verdoux et al., 1997), poor premorbid social and occupational adjustment (Foerster et al., 1991) premorbid personality disorder and being unmarried (Jablensky and Cole, 1997). The reported sex difference in (AOO, has been reported to be an artefact of other confounding variables including marital status and premorbid personality, delaying AAO in men more so than in women (Jablensky and Cole, 1997). Castle et al. (1998) found that the significant predictors of early AOO were poor premorbid occupational

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functioning, single marital status and male sex. Some studies have reported that unlike men, women display a bimodal age distribution, with a second peak occurring in middle age. Approximately 3 to 10 percent of women present with disease onset (late-onset) after age 40. It is suggested that women with late-onset of the disorder represent a different prototype of schizophrenia than males with early onset (Lewine, 1981; Hafner et al, 1993, 1998). A major flaw of these studies when comparing men and women with schizophrenia, however, is that they imposed an age cut-off. For example the ABC study by Hafner and colleagues (1993) did not include patients with an onset over the age of 59 years, which has a marked preponderance of women (Castle, 2000). One study by Castle et al, (1998), however, reported differences in the onset distribution between men and women, revealing a two-peak distribution in men, and a three-peak distribition in women. The distribution of AOO for men were: 21.4 years and 39.2 years, and for women they were 22.4, 36.6 and 61.5 years.

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Men with schizophrenia may have a poorer premorbid history, worse response to antipsychotic medications, worse outcome, more negative symptoms and more structural brain abnormalities compared to women (Andreasen et al., 1990; Goldstein et al., 1995; Lewine et al., 1995; Goldstein et al, 1995). Ring et al (1991) noted that negative symptoms were twice as severe in men compared to women, as rated by the Scale for Assessment of Negative Symptoms (SANS), although men and women did not differ in the severity of their positive symptoms, as rated by the Present State Examination (PSE). However, in a group of first episode schizophrenic patients, Szymanski et al. (1995) reported that women demonstrated significantly less illogical thinking, but more anxiety, inappropriate affect and bizarre behaviour. In addition, Andia et al. (1995) found that schizophrenic women were diagnosed more frequently with the paranoid and disorganized subtypes of schizophrenia than men, who were more likely to fulfil the criteria for undifferentiated schizophrenia. Developmental issues have also demonstrated significant gender differences. Goldstein et al. (1994) reported that men with schizophrenia are at a greater risk for exhibiting a history of childhood developmental anomalies, in comparison to women with schizophrenia.

Based on these reports, Goldberg et al., 1995 offered a hypothesis that female schizophrenics assume a milder disease form and suffer less cognitive impairment than their counterpart males during the course of the illness.

Lewine et al. (1997) have proposed that the epidemiological sex differences in schizophrenia may represent variations in aetiology. Greater genetic (nonsporadic) and hormonal influences have been suggested in women (Goldstein et al., 1990; Hafner et al., 1991, Goldstein and Tsuang, 1990) and greater non genetic (sporadic) brain structural involvement in men (Raz and Raz, 1990).

2.2 Neurocognitive Deficits in Schizophrenia

In the previous section (section 2.1), sex differences within the disorder were described. The following sections will discuss neurocognitive deficits in schizophrenia and sex differences in these deficits in the cognitive domains of spatial, verbal, cognitive inhibition, and working memory. Studies of cognition in schizophrenia have parsimoniously assessed deficits in general neurocognitive functioning. For example, verbal fluency and mental rotation are examined as part of a larger battery of cognitive tests which assess brain functioning in patients, but do not necessarily look for sex differences in the performances on the psychometric tasks. There exists a paucity of literature considering the sex differences; and therefore general neurocognitive deficits in patients with schizophrenia will be discussed, followed by studies that have examined the sex differences in cognitive functioning in schizophrenia.

A substantial number of neuropsychological studies demonstrate that patients with schizophrenia in comparison to healthy normal control subjects are pervasively impaired on tests which correspond to the domains of executive functioning, verbal/language abilities, verbal memory and delayed non-verbal memory, and spatial memory (Riley et al., 1999; Sweeney et al., 1991, 1992; Bilder et al., 1992; Hoff et al., 1992; Saykin et al., 1994; Censits et al., 1997; Bilder et al., 2000; see also, Henrichs and Zakanis, 1998 for review).Unfortunately, there can be confusion within the literature of what is the `optimal

test` for measuring the functioning of the domains. Neuropsychological studies of schizophrenia usually employ different tests to assess the same domains of cognitive functioning. One study may use the Wisconsin card-sorting test (WCST; Heaton, 1983) to measure executive functioning whereas another study may use the Stroop test to assess the same cognitive domain. Alternatively, others may use the Stroop to measure attentional factors. Some tests (such as the Stroop) can measure more than one cognitive domain (executive functioning and attention in this case) and this can sometimes lead to difficulties in the interpretation of the observed data. For this purpose, the author will briefly provide an overview of the core tests that are used in neuropsychological studies in schizophrenia as well as the corresponding deficits they represent.

Patients with schizophrenia appear to perform poorly on the WCST, which is a measure of executive functioning. Failure to perform well on this task is indicative of the inability to form abstract concepts and carry out effective cognitive shifting to perform flexible thinking. Poor performance on this task is also suggestive of deficits in the prefrontal cortex (PFC). The Stroop colour word test, the WISC-R (Weschler Intelligence Scales for Children –Revised) and the Trails B, are used as measures of executive functioning. Poor performance on this task is indicative of the inability to form and initiate a strategy, to inhibit prepotent responses, as well as being unable to shift cognitive set. Additionally these tests also require intact attentional processes. Furthermore, impaired performance on the Stroop test is also indicative of deficits in the ability to ignore relevant stimuli and to pay attention to less important ones. Verbal memory deficits (which are found in poor performance on tests such as the Rey Auditory Verbal Learning Test (Rey, 1964), Bushke Selective Reminding test (Bushke, 1973), Hopkins Verbal Learning test (Brandt and Benedict, 1999) and the Logical Memory story recall; Weschler Memory Scale-Revised) demonstrate the inability to learn and retain verbal material over time, and also imply deficits in attentional processes (Mirsky and Duncan, 1986). These tests tend to represent brain functioning in left temporal regions. Another cognitive domain where patients demonstrate impaired performance is that of verbal abilities; in particular, in phonological and category fluency tasks. Deficits are thought to be suggestive of patients experiencing greater difficulty with semantic cueing of retrieval. Similar to verbal

memory, verbal abilities have been associated with left frontal functioning. However, poor performance on verbal working memory tests such as the Letter-Number Test (Gold et al, 1997) suggests an inability to retain and manipulate common verbal stimuli in working memory. In the same way, poor performance on tests that measure visuo-spatial working memory such as the Benton Visual Retention Test (BVRT; Benton, 1972) demonstrates the inability to maintain and manipulate spatial representations in working memory. Both these tests tend to rely on areas of the PFC, in particular the dorsal lateral prefrontal cortex (DLPFC). Neuropsychological studies have also demonstrated deficits in sustained attention in patients with schizophrenia. Poor performance on tests such as the continuous performance test (CPT; Cornblatt et al., 1988) is indicative of impaired attention and the inability to focus on critical stimuli. Poor performance on tests that measure visuo-motor skills, such as Trails A (Reitan, 1958), groove pegboard and the Finger tapping test (Halstead, 1947) demonstrate deficits in visuo-motor tracking and motor coordination. Speed of information processing assessed by tests such as the Speed and Capacity of Language Processing (SCOLP; Baddeley et al., 1992) demonstrates the slowing of cognitive processing associated with schizophrenia by assessing language comprehension.

Neuropsychological deficits are a core feature of schizophrenia, which may influence positive and negative symptoms in the aetiology of the disorder (e.g. Gold and Harvey, 1993). A number of studies in the schizophrenia literature have reported low premorbid IQ's in patients with schizophrenia. Although a number of findings suggest that patients with schizophrenia experience intellectual decline following onset of the illness (Goldberg et al., 1988; Goldberg et al., 1993; Nelson et al., 1990), some studies have reported that intellectual deterioration predates the onset of schizophrenia, and this then predisposes to further IQ decline (Russell et al, 1997) at around the time of their first illness. Several reports have documented lower premorbid IQs in children who later develop schizophrenia (Torrey et al., 1994; Aylward et al., 1984; Munro et al., 2002). Weickert et al. (2000) tested 117 patients with schizophrenia and 27 healthy controls on a neuropsychological battery to investigate patterns of premorbid (Wide Range Reading Test Revised; WRAT-R) and current IQ (WAIS-R), as well as the attendant cognitive

profiles using classification methods based on clinically derived (IQ) levels and atheoretical (cluster) techniques. The authors reported that sixty patients (51%) with schizophrenia, who exhibited a general intellectual decline of 10 points or greater from estimated premorbid levels in comparison to the control group, also showed deficits of executive functioning, memory and attention. Furthermore twenty-eight patients (23%) with consistently low estimated premorbid intelligence and current IQ, who displayed no evidence of IQ decline, exhibited language and visual processing deficits in addition to the deficits present in the intellectually declining group. Twenty-nine patients (25%), who displayed average estimated premorbid intellectual levels, did not show IQ decline and exhibited a cognitive profile similar to the normal group, with the exception of executive function and attention impairment.

Several studies have looked at the cognitive profile of patients with first episode schizophrenia (Sweeney et al., 1991, 1992; Bilder et al., 1992; Hoff et al., 1992; Saykin et al., 1994; Censits et al., 1997; Riley et al., 1999). Saykin et al (1994) investigated neurocognitive deficits in three different groups; 1) neuroleptic naïve patients with first episode schizophrenia, 2) unmedicated, previously treated patients and 3) healthy controls. They found that both patient groups had nearly identical cognitive profiles, with generalised impairment, particularly in verbal memory and learning, attention-vigilance, speeded visual motor processing and attention. In addition, they reported that verbal memory accounted for most of the variance between patients and controls, this deficit remaining in both patient groups after controlling for all other cognitive tests. An interesting finding of this study was that cognitive functions not usually implicated in schizophrenia (spatial cognition, fine motor speed and visual memory) were more impaired in the previously treated patients, suggesting a possible role of medication, attenuating the effects of these abilities.

The above review of the literature would suggest consensus that a pervasive impairment in cognitive performance in schizophrenia exists. However there appears to be some discrepancy as to whether the neurocognitive impairment is general, affecting all cognitive domains, or whether it is restricted to certain domains. Findings from studies of

neural pathology in schizophrenia show widespread neuroanatomical abnormalities. However, reports in psychiatric literature have suggested that patients with schizophrenia demonstrate specific deficits that are imbued in the context of more generalised impairment. Saykin et al (1991) reported generalized cognitive impairment in a group of unmedicated patients with schizophrenia, compared to age-matched controls. In particular, a selective deficit in memory and learning (paired associate learning, CVLT, Logical memory (WMS immediate and delayed) compared with other cognitive functions was demonstrated. However, they found no selective impairment on tests related to frontal functioning (abstraction, verbal fluency and motor tests). These findings were hypothesised to be suggestive of involvement of the temporal-hippocampal system, against the background of diffuse dysfunction. Hoff et al. (1992) compared 32 patients with first episode schizophrenia, 26 patients with chronic schizophrenia and 25 healthy comparison subjects on a neuropsychological battery. With age and education controlled, they found both patient groups to be impaired on the neuropsychological composite measures of executive functioning, verbal memory, spatial memory, concentration/speed, global cognitive function, and on left and right hemisphere function scales, compared to the normal control group. Interestingly, both groups showed relatively greater left than right hemisphere dysfunction. Several studies have demonstrated impaired performance on verbal fluency tasks in schizophrenia (Kolb and Whishaw, 1983; Gruzelier et al., 1988; Allen et al., 1993). Riley et al (2000) examined the neuropsychological profile of a group of patients with first episode schizophrenia (N =40) and matched controls (N=22). The results showed impaired performance on measures of executive functioning, psychomotor speed, and verbal fluency, as well as on verbal learning and delayed non-verbal learning. The authors suggested that deficient performance on psychomotor speed was indicative of cognitive slowing at the first onset of psychosis. Joyce et al. (1996) examined whether poor verbal fluency in schizophrenia represents a degraded semantic store, or inefficient access to a normal semantic store. In a group of 50 patients with a diagnosis of schizophrenia and 25 matched controls (age, sex and IQ), they compared performance of letter and category fluency, examining the response to cueing by using a modified version of the method used by Randolph et al. (1993). They reported that although patients with schizophrenia were impaired on both letter and category fluency,

they showed a normal pattern of output in that category fluency was superior to letter fluency. The patient group also showed an improvement in category fluency when the cueing method was employed. The authors concluded that poor verbal fluency in schizophrenia is due to inefficient access to semantic store.

Impaired performance on working memory tasks in patients with schizophrenia has been found to be greater than that of patients with other neurological disorders, that are matched for age, sex and premorbid intellectual ability (IQ measured with the National Adult reading Test; NART, Pantelis et al., 1997). Furthermore, schizophrenic patients have been shown to have larger deficits in working memory performance in comparison to other memory deficits (e.g long-term memory). Sullivan et al. (1997) demonstrated that performance on verbal working memory tasks was found to be 4 standard deviations below the normal mean, whereas performance on the long-term memory tests (e.g. recognition) was only 1 standard deviation below the normal mean in a group of patients with schizophrenia. In another study, Bryson et al. (2002) sought to investigate the longitudinal pattern of executive functioning in schizophrenia. They measured cognitive performance using the WCST and the digit symbol substitution sub-test of the WAIS-R, establishing whether there was deterioration, improvement or stability over time in a group of patients (N = 46) with schizophrenia or schizoaffective disorder, in a stable phase of illness and actively involved in rehabilitation. The cognitive assessments were conducted at two time points, on average 4.3 years apart. The results demonstrated that there was stability in most WCST variables; however, patients demonstrated a significant improvement on WCST perseverative errors and on the digit symbol substitution test. Sixty-five percent of the group showed improvement on one or both of the test variables. These improvements were found to be unrelated to the type of antipsychotic medication, and were only modestly related to symptom variables. The authors concluded that WCST performance is generally stable over the 3-7 year time period in stable patients with schizophrenia.

A longitudinal analysis of symptoms and neuropsychological functioning in patients (N=62) with chronic schizophrenia demonstrated that the severity of negative symptoms

predicted poor IQ as well as poor performance on verbal fluency and memory at baseline (Hughes et al., 2003). However, significant improvements in symptom scores did not predict improvements in any aspect of neuropsychological functioning. Penades et al. (2001) examined the role of clinical and neuropsychological variables on psychosocial functioning and evolution of negative schizophrenia in a group of chronic schizophrenic outpatients (N=49) who were pharmacologically stabilized. The researchers established two groups of patients with similar psychopathologies, but with different neuropsychological and prognostic characteristics. Impairment on neuropsychological tasks was significantly related to a poorer prognosis, poorer evolution, and inferior psychosocial adaptation. Albus et al. (2002) investigated temporal stability of neuropsychological impairment in a group of first episode patients with schizophrenia (N=50) and healthy controls (N=50), matched for age, sex, education and parental socioeconomic status. These subjects were administered a cognitive battery at baseline, and then again after a two-year interval. Summary rating scales demonstrated improvement in verbal learning (VBL), stable function of semantic memory (SEM), visual motor processing and attention (VSM) and abstraction/flexibility, and no improvement was reported on the visual memory (VIM) domain. The authors suggested that, whilst performance on the VSM and VIM is influenced by medication status, SEM appears to be trait-related and stable, whereas VBL seems to be state-related. The data suggests that that there is not enough data to prove that progressive deterioration occurs in neuropsychological functioning during the first few years of illness. Another study (Fuller et al., 2002) conducted a longitudinal assessment of premorbid cognitive functioning in patients with schizophrenia, based on prospective data obtained from scholastic test results. The authors collected scores from grades 4, 8 and 11 on the Iowa Tests of Basic Skills and Educational Development in 70 participants who later developed schizophrenia. The mean percentile rank of the participants' scores in the areas of vocabulary, reading comprehension, language and mathematics were compared with state norms. The results demonstrated that the participants scored below the 50th percentile for all the categories in all three grades, but only language and reading scores were significantly below state norms from grade 11. Over the longitudinal course, there was a significant linear decrease in language scores. The grades at which tests scores

dropped corresponded to ages 13-16, or the onset of puberty. Fuller et al, (2002) concluded that declining scholastic performance may be a precursor to the cognitive impairment seen during the first episode of illness.

2.2.1 Sex Differences in Neurocognitive Performance in Schizophrenia

There is, within the literature, a paucity of studies that have investigated sex differences in neuropsychological performance in people with schizophrenia. Furthermore, there have been no studies to date that have investigated differences between schizophrenic men and women on a sexually dimorphic cognitive battery.

Studies of sex differences in neuropsychological performance in schizophrenia continue to report disparate results. Authors such as Haas et al., (1991); Goldstein et al., (1994, 1995); Hoff et al. (1995); Hoff et al., (1998); Seidman et al.(1997), report men to exhibit greater cognitive impairment compared to women. On the other hand, other authors describe greater cognitive impairment in women (Perlick et al., 1992; Lewine et al., 1996). In contrast to these findings, Hoff et al., (1992); Andia, et al., (1995); Goldberg et al., (1995) report no sex differences in cognitive performance between men and women with schizophrenia. These studies are comprised of both first episode schizophrenic patients (Hoff et al., 1992; Hoff et al., 1998) as well as chronic schizophrenics (Perlick et al., 1992; Andia et al., 1995; Goldberg et al., 1995; Lewine et al., 1996; Hoff et al., 1998).

Bilder et al. (1992) investigated IQ profile in first episode and chronic patients with schizophrenia. They found although total IQ scores did not differ between the sexes, men showed more evidence of deterioration than women when their sub-scale patterns were compared. This finding, however, was limited by the use of cross-sectional design and did not consider the temporal pattern. Haas et al. (1991) found no sex differences in cognitive impairment of first episode patients, but in patients who had been ill for 5 years or longer, men showed greater deficits on verbal tasks (thought to represent greater left

hemisphere dysfunction). Seidman et al. (1997) showed that male patients with schizophrenia performed worse than women on the WCST, suggestive of greater dorsolateral prefrontal deficits. A recent study (Goldstein et al., 1998) reported male patients to be significantly impaired across all cognitive functions, in comparison with female patients, on tests of attention, verbal memory, and executive function (the three domains thought to be central in the neuropsychology of schizophrenia). Female patients were found to perform significantly worse than female normal comparison subjects only on tests of attention, executive functions, visual memory, and motor functions, whereas the male patients performed worse on all cognitive functions in comparison to the male control group. The authors concluded that women with schizophrenia might be less vulnerable to particular cognitive deficits, especially those involving verbal processing, than schizophrenic men. Furthermore, Goldstein et al (1998) projected the hypothesis that schizophrenic men may be at higher risk than women with schizophrenia for more severe neurocognitive consequences, because of early developmental deficits. This would seem to be in concordance with other studies examining the sex differences in high-risk subjects for schizophrenia in neurocognitive and neurodevelopmental function during early development. These subjects exhibited significantly more premorbid abnormalities amongst boys in comparison to girls in neuromotor function, aggression and social withdrawal, (Marcus et al., 1987), impulse control and IQ, electrodermal response (Aylward et al., 1984) and attention (Erlenmeyer-Kimling et al., 1984). Correspondingly, other studies indicate that men with schizophrenia have greater impairment of sustained attention, language, executive functions, intelligence and olfactory identifications, in comparison with female schizophrenics (Seidman et al., 1997, Goldstein et al., 1994; Haas et al., 1991; Kopala and Clark, 1990). Hoff et al. (1998) tested both first episode and chronically ill men and women with schizophrenia and a control group on a cognitive battery. After adjustment for age, age at onset and premorbid IQ, they found that male chronic patients performed worse than female chronic patients on the spatial memory domain (BVRT and visual reproduction). However, after controlling for symptom severity, this sex difference finding became non significant. Albus et al. (1997) examined sex differences in a group of first episode patients with schizophrenia (20 men, 20 women, matched for age and education) and

found that women performed better than men on tests measuring verbal memory and learning, and men performed better than women on spatial organisation. Sex differences in sex-onset effects on neuropsychological functioning in schizophrenia have demonstrated poorer performance and less lateralized function in early-onset men and late-onset women compared with late-onset males and early onset females (Lewine et al, 1997). The results of Lewine et al.'s study suggested that there is greater neuropsychological impairment in early onset men than in late onset men, but less neuropsychological impairment in early onset women than in late onset women. Perlick et al. (1992) found that female inpatients performed worse than male inpatients on attention and conceptualisation tasks. On construction tasks, female inpatients scored worse than male inpatients. Similarly, Goldberg et al. (1995) found that men and women performed identically on nearly all of the 100 neuropsychological test measures, and on those measures that showed a significant sex difference, males performed better than females. An outpatient study by Andia et al. (1995) reported a lack of sex differences in IQ and expanded Halstead–Reitan Battery scores; and further reported that there were no differences in age of onset in their study.

Some studies which have examined the neurocognitive profile of patients with schizophrenia may have been influenced by the possibility that the impairment could be a sequelae of long term treatment, either treatment with conventional antipsychotics (as opposed to atypical agents), or long-term institutionalisation, rather than the processes of the disease itself (Riley et al., 1999; Saykin et al., 1994). However, Gold and Weinberger (1995) argue that neuropsychological impairment appears to be a relatively stable feature of the illness and therefore independent of neuroleptic treatment, whereas symptom states fluctuate dramatically among patients and respond (variably) to neuroleptic treatment. Furthermore they postulate the possibility of dissociation of the neurobiology for these dimensions of schizophrenia.

Inconsistent findings in studies of sex differences in schizophrenia may be due to sampling strategies and inadequate sample sizes to detect for sex effects (Walker et al., 1993). Some studies have had methodological limitations; failing to account for age at

onset or illness severity, not including normal comparison groups, and having used relatively small and heterogeneous samples (Goldberg et al., 1995, Lewine et al., 1996). In addition, it is important to note that sex differences that are found in schizophrenic patients may be representative of premorbid sex differences, which then lead to sex differences in cognitive performance during the process illness (Goldstein, 1998).

In summary, the literature reports that patients with schizophrenia exhibit deficits in attention executive functions, verbal and visual memory recall, working memory, visuo-spatial abilities and fine motor skills. The main brain areas that are involved in these cognitive processes are the medio-temporal and prefrontal cortical regions, the motor cortex and the basal ganglia (Frith, 1995). The most likely explanation is that cognitive impairment in schizophrenia reflects diffuse brain dysfunction, rather than putative structural defects (Saykin et al., 1994). Findings with regard to sex differences in neurocognitive functioning are inconsistent, some showing greater cognitive impairment in men and others in women. Also, studies report differential deficits in cognitive domains that are dependent on whether patients suffer a chronic form of the disease or if they are experiencing a first episode of the illness.

2.3 Schizophrenia, Gonadal Hormones and Symptomatology

There are several reasons for studying the effects and mechanisms of action of certain gonadal hormones (E and T) in psychiatric disorders. Firstly, there are gender-related differences in the prevalence, course and treatment response characteristics of several psychiatric disorders; for example, females show a greater prevalence of depression and a lesser prevalence of learning disorders (Weissman et al., 1988; Tallal, 1991; Geshwind and Behan, 1982). In schizophrenia, women demonstrate a later onset of schizophrenia by about 3-4 years, in comparison to men (Hafner et al., 1992) but this is only true if the illness starts after puberty (Galdos et al., 1993). The delayed onset of schizophrenia in women has been attributed to the protective effect of E on the central nervous system (Hafner et al., 1992, 1998, Seeman and Lang, 1990.) The following section will discuss

the role of E and T in the clinical and cognitive presentation of schizophrenia in men and women.

The observation that there is a later onset of schizophrenia in young women compared to men and that the incidence rises during the menopause period, stimulated interest in the role of gonadal hormones such as E in the pathogenesis of the disorder. The 'estrogen hypothesis' in schizophrenia and related psychosis assumes that E plays a protective role in delaying the onset of schizophrenia in women with a severe disposition to the disorder. This suggests that the initiation of cyclical hormone fluxes in women may serve as a protective function against the development of adolescent psychosis. This hypothesis is further reinforced by the observation that, whereas men exhibit one main peak of schizophrenia onset in their late teens and early twenties, women show an additional onset peak at age 40-45 years, which is a time when E levels are falling (Hafner, 1993).

Hafner et al. (1998) conducted a series of experiments to investigate the causes and consequences of the sex difference in age at onset of schizophrenia. In one of these studies they investigated women with acute schizophrenia (N= 32) and a control group (N= 29), assessing their psychopathology (including depressive features) and with both groups having normal menstrual cycles. They examined the participants at six defined days of their cycle. Each time they did so, they measured serum E levels and other hormonal parameters. They found a significant negative correlation between E levels or the corresponding menstrual phase and schizophrenia, and a significant negative correlation with non-specific symptomatology. However, they found no correlation between E levels and measures of depressive symptoms in either group. They concluded that the neuromodulatory effect of E may play a protective role in schizophrenia and could be a potential factor in delaying onset in women. Hafner et al. investigated the role of E further, hypothesising that 1) if women are protected by E until premenopause then they should, from that age on, show higher incidence rates of schizophrenia than men and, 2) older aged women should also present with more severe forms of the disorder than men of the same age. The investigators stratified a sample of patients with first episode psychosis into three groups by age of the first presentation of positive symptoms.

The groups consisted of: Group 1, subjects under 21; Group 2, adults between the ages of 21-35, and Group 3, adults between the ages of 36 and 60. They found that women predominated significantly in the oldest group; and concluded this represented higher incidence rates of late-onset schizophrenia in women in comparison with men. They felt this was consistent with the first hypothesis. Also, the authors found evidence of their second hypothesis, in that late onset schizophrenia in women was more severe compared with late onset male schizophrenics, but it was not less severe than female early onset schizophrenia. Stevens (2002) suggested that the ages of onset of schizophrenia closely parallel the ages at onset and the decline of the reproductive period. She explicated that the reproductive period is associated with development of regular pulsatile release in the brain and bloodstream of gonadotropic releasing hormones from the hypothalamus, LH (increases more than 30-fold in boys and 100-fold in girls) and FSH from the pituitary, and gonadal hormones (E and T) from the ovaries and testes, both known to be excitatory hormones. As well as being expressed in the hypothalamus, brain receptors for gonadotropic and gonadal hormones are concentrated in specific subcortical forebrain nuclei of the limbic system (medial amygdala, the bed nucleus of stria terminalis, and lateral septum in the basal forebrain) that project to the thalamus and to cortical and subcortical structures that underlie perception, cognition and behaviour. In order to avoid hyper-excitability, Stevens argued that the surge of these excitatory hormones into the specific brain areas at puberty and throughout the reproductive period need to be counterbalanced by appropriate inhibitory factors, such as an increased release of (or increased receptors for) one or more inhibitory neurotransmitters such as DA and serotonin in the anterior basal forebrain. However, excessive inhibitory response to these physiological events via DA, 5-HT or GABA can cause psychosis in susceptible individuals. Lindamer et al., (1999) examined gender-related clinical differences in older (46-85 years of age) patients with schizophrenia. They compared the clinical characteristics of men and women with early onset schizophrenia (N=90) to those with late onset schizophrenia (N=34). The authors concluded that women overall may develop more severe positive symptoms than men, and that when women develop schizophrenia after age 45, they may suffer less severe negative symptoms than men or than women with earlier onset; however, women with late onset had significantly less severe negative

symptoms than men with early onset, or men with late onset. Additionally, Seeman (1996) suggested that the severity of illness expression in women is less debilitating than in men during the first decade following onset.

Several other bodies of evidence are discussed below to examine the role of E in schizophrenia. Effective response to standard neuroleptics is said to take place at lower doses in women, at least premenopausally (Seeman, 1983). Postmenopausally, women require higher maintenance doses than men. This has been attributed to the potentiating effect of the antidopaminergic action of E on neuroleptic response (Hafner, 1993). Sex and age differences in extrapyramidal side effects and tardive dyskinesia also suggest possible hormonal effects (Yassa and Jeste, 1992), especially since tardive dyskinesia is alleviated by E treatment in both sexes (Nelson et al., 1995). Kulkarni et al. (1995) reported that the administration of 0.02mg E to premenopausal women with schizophrenia or schizoaffective disorder for one month, in conjunction with standardized neuroleptics treatment, decreased the total score on the SAPS to a greater extent than in a comparison group of women who received neuroleptics only. At the end of the 2-month treatment with E, however, the scores on the SAPS increased. Kulkarni`s group concluded that E might enhance the effects of neuroleptics to reduce positive symptoms initially, but that this effect might be reversed with longer administration of E. In later studies, Kulkarni et al., (1996, 2001) reported that E given as adjunctive with neuroleptic treatment to women with acute psychotic illnesses resulted in a decrease in positive and overall psychiatric symptoms compared to women on neuroleptics alone. In a preliminary open clinical trial, Kulkarni (1996) compared 11 women with acute psychotic symptoms, with added 0.02mg E to neuroleptic treatment for eight weeks, to 7 women taking neuroleptics treatment alone. They reported women taking the E adjunct showed a more rapid improvement in psychotic symptoms, compared with the group receiving neuroleptics alone. However, this effect was not sustained for the entire trial; by the eighth week, both groups reached similar levels of recovery. Similarly, in a double-blind placebo controlled trial, Kulkarni et al. (1999) reported that 2mg of estradiol valerate as an adjunct to standard neuroleptics with risperidone improved psychotic symptoms (tested at day 0, 3 and 7) in two groups of 5 men with

schizophrenia. Kulkarni et al. (2001) conducted a double blind 28-day placebo controlled study with three groups of women of childbearing age, who were on standardised antipsychotic treatment plus either 1) 50mcg E (N=12), (2) 100mcg E (N=12) or, 3) placebo (N=12), all administered transdermally. They found that women receiving 100mcg of E made greater improvements in symptoms of schizophrenia, compared with the other groups. This group also had lower levels of LH and higher mean PROL levels compared with the other groups. Villeneuve et al. (1980) administered E tto men and women with schizophrenia, and examined their extrapyramidal symptoms. E treatment resulted in a slight reduction in the intensity of dyskinetic movement, but the Parkinsonism was not affected by E. Lindamer et al. (2001) tested a group of postmenopausal women with schizophrenia who had received (N=24) versus never received (N=28) HRT. They found that HRT users required lower doses of antipsychotic treatment, independent of differences in antipsychotic dosage. Both groups had similar levels of positive symptoms; however, the HRT group had less severe negative symptoms. The results were further strengthened, as the groups did not differ with respect to age, ethnicity, education, age of onset, duration of schizophrenia and global cognitive functioning.

The beneficial role of E has also been demonstrated in menstrual cycle studies. Symptoms of schizophrenia have found to be exacerbated at low E phases of the menstrual cycle (Endo, 1978), whilst high levels of E over the menstrual cycle have been reported to reduce psychopathology ratings in a similar way to neuroleptic medication (Seeman and Lang, 1990; Riecher-Rossler et al., 1994; Hallonquist et al., 1993; Gattaz et al. 1994). Riecher-Rossler et al. (1994) found an improvement in positive symptoms during the high E phase of the menstrual cycle in a group of 32 women with schizophrenia. Hallonquist et al. (1993) studied severity and types of psychopathology in 5 outpatient women (aged between 29-49) with schizophrenia, over two consecutive menstrual cycles. All the females had regular menstrual cycles and were receiving antipsychotic treatment. They found a reduction in the scores for the global psychopathology scores during the high E phase of the menstrual cycle, and the reverse was found during the low E phase. However, in this study, no blood levels were taken to

obtain a measure of E. Gattaz et al. (1994) compared 65 women with schizophrenia to 35 women with affective disorder (both groups aged between 18-45) on admission to hospital. All of the women had regular menstrual cycles. The women were dichotomised into low and high E phase. The authors found more women were admitted during the low E phase, and that these women also required significantly lower mean daily doses of antipsychotic treatment, compared to those admitted during the high E phase of the menstrual cycle. Thompson et al. (2000) investigated the severity of neuroleptic side effects in women with psychosis (N=25) and examined their possible association with variations in gonadal hormones over the menstrual cycle. They found higher levels of E reduced hyperkinetic symptoms, and this effect was potentiated when E and progesterone were high.

Huber et al. (2001) examined E levels in psychotic disorders in a group of 43 women admitted with a diagnosis of an acute psychotic episode. When assessing their cycle phase on admission to hospital (by hormone level), 56% of the women were found to be admitted during the low E phase of the menstrual cycle, as opposed to 28% who were admitted during the peri- or postovulatory phase (high E). E levels were however below the normal reference range in this sample of patients including the peri- or postovulatory phase. In a more recent study, Liao et al. (2002) reported that three-month E treatment in 4 female chronic patients with schizophrenia, on atypical antipsychotic treatment, resulted in an attenuation of premenstrual aggravation of psychiatric symptoms during menstruation in two of the four patients. However, the authors found that after discontinuation of E treatment, three patients were assessed as worse than pre-E treatment using the Nurses' Observation Scales for Inpatient Evaluation. The authors suggested that there may be individual variability for response to E treatment. However, because of the small sample size in this study, caution must be shown when trying to generalise these findings.

There is also some evidence that higher levels of E during pregnancy may protect females from psychosis. Women with a diagnosis of schizophrenia have been shown to have an improvement in their symptoms during pregnancy and to have a vulnerability to

psychosis in postpartum period when E falls (Lindamer et al., 1997). Furthermore there are reports of an increase in psychiatric hospitalisations for psychosis postpartum relative to antepartum (Kendell et al., 1987). Kendell et al. (1987) reported that hospital admissions for psychosis related to depression or schizophrenia, within the postpartum period, were 21.7 times more likely in the first month and 12.7 times within 3 months in comparison to the antepartum period.

The clinical features of schizophrenia in young women with long-standing hyperandrogenism related to polycystic ovarian disease provide additional evidence of the E hypothesis. Based on observations of a young woman with hyperandrogenism, it was reported that hyperandrogenism contributed to a relatively early onset and other clinical features of schizophrenia more commonly associated with men. Kopala et al. (1997) hypothesised that acute E depletion following cessation of oral contraceptives may precipitate psychosis, while recommencement of oral contraceptives may contribute to subsequent improvements in symptoms.

DiPaolo et al (1981) suggested that E treatment or high levels of E might have a direct neuroleptic effect via a membrane effect on the presynaptic DA2 receptor. This was further supported by the publications of DiPaolo et al. in 1994 and McDermot et al., also in 1994. However, a PET study by Nordstrom's group in 1998, examining whether different levels of gonadal hormones during the menstrual cycle are associated with variations in dopamine (DA) D2 receptor density, found no support for the hypothesis of menstrual cycle dependent variation in DA2 receptor density in a group of 5 healthy women.

The neurohormonal mechanism through which E affects symptoms is not yet clear. However, there is evidence that E acts on the same neurotransmitter systems as the antipsychotic medications, that is, the blockade of dopamine (DA) DA2 receptors by traditional neuroleptics (Riecher-Rossler and Hafner, 1993). Like E, classic neuroleptics reduce acute symptoms in schizophrenia and delay relapses, but do not reduce the lifetime risk (Seeman and Lang, 1990). In addition, E has been reported to have dose

dependent effects on the modulation of dopaminergic systems (DiPaolo et al, 1981). It has been suggested that, since antipsychotic medications block the dopamine D2 receptor, the antidopaminergic properties of E may help explain why younger females with schizophrenia appear to require lower medication doses and have a better treatment response than older women do (Seeman, 1996). In a three-year survey, Seeman (1983) found that mean chlorpromazine equivalent doses were similar in men and women, while younger women (20-39) were maintained on lower doses than their male peers who had been matched for age. After the age of 40, women required higher doses than men. However, Salokangas (1995) failed to replicate this finding that there was a usage of lower medication doses in younger women and higher doses in older women. In this study, a group of 1097 patients with schizophrenia were discharged from hospital, and their daily doses of neuroleptic drugs were recorded for three years. The results showed that only middle-aged groups of male patients used higher daily doses of neuroleptics in comparison to the female patients. Daily doses were also associated with age at the onset of illness, duration of illness and clinical status. In women, they found no consistent increase in daily doses of neuroleptics treatment after the menopause age.

Animal studies have also provided evidence for a positive role of E, via its effects on different neurotransmitter systems; for example, E has been shown to modulate dopamine (DA) and serotonin neurotransmitter systems, the main neurotransmitters implicated in the pathogenesis of E. In particular, E has been reported to reduce the DA concentration in the striatum and modulate the sensitivity of the DA receptors (Foreman and Porter, 1980; Koller et al., 1980; Gordon et al., 1980; Dupond et al., 1981). Summer and Fink (1995) showed that E treatment in castrated rats leads to significant agonistic effects on the serotonin transmitter system. Woolley and McEwen (1994) suggested that E might also act on N-methyl-D-asparate receptors. Fink et al. (1998) and Summer and Fink (1998) demonstrated that E and T (enzymatic conversion by aromatase to E) can modulate serotonin systems by increasing the expression of genes for the 5-HT2A receptor and the serotonin transporter in the dorsal raphe nucleus and forebrain, regions associated with the control of mood, mental state and cognition. It has also been suggested that the presence of T, which is aromatised to E in the brain, affects the

process of brain lateralization, and may influence brain organisation (Naftolin and McLusky, 1984).

2.3.1 Relationship Between Prolactin (PROL) and Symptomatology in Schizophrenia

Several studies have reported dysregulation of stress hormones in schizophrenia. It is well known that treatment with neuroleptics can cause hyperprolactinemia (Meltzer et al., 1976, Gruen et al., 1978; Green and Brown, 1988; Dickson et al., 1995). The principle action of the pituitary hormone PROL is to initiate and sustain lactation, and it is involved with some aspects of gonadal function.

A debilitating side effect of antipsychotic medication in patients with schizophrenia has been the elevation of the hormone PROL. PROL is secreted by the anterior pituitary but is primarily under tonic dopaminergic (DA) inhibitory control (Kato et al., 1985) and is released from the tuberoinfundibular neurons originating in the arcuate nucleus. DA demonstrates its inhibitory effect on PROL via DA2 receptors located on the pituitary lactotrophs. The main target for conventional antipsychotic treatment is predominantly at the DA2 receptors, which can result in hyperprolactinemia. Since the release of PROL is tonically inhibited by the hypothalamus, with DA acting as the PROL release inhibiting factor, any disruption of the connection between the hypothalamus and the pituitary gland is associated with hyperprolactinemia.

The clinical manifestations of hyperprolactinemia in women are amenorrhea, cessation of normal cyclic ovarian function, loss of libido, galactorrhoea, obesity, occasional hirsutism, and increased long-term risk of osteoporosis. The effects in men are impotence, loss of libido and hypospermatogenesis. Typical antipsychotics, as well as the novel antipsychotic risperidone, are known to elevate serum PROL levels (Canuso et al., 1998; Dickson et al. 2000). While women normally have slightly higher PROL levels than men, PROL elevation in response to antipsychotic treatment is notably greater in

women than men (Meltzer et al., 1983). With conventional antipsychotic medication, an established correlation exists between occupancy of striatal DA receptors and plasma PROL levels (Baron et al., 1989), which indicates that these agents lack specificity of DA blockade. Some evidence suggests that women treated with antipsychotic medication have diminished E levels, perhaps mediated by sustained PROL elevation (Reicher-Rossler et al., 1994).

E has been shown to inhibit DA synthesis in the tubero-infundibular dopaminergic neurons (Arita and Kimura, 1986, 1987) and modulate both the amplitude of spontaneous PROL bursts (Veldhuis et al., 1989) and the activity of striatal dopamine (Ramos et al., 1987), all of which may contribute to some of the sex differences in neurocognitive function, and to the clinical manifestation of psychiatric disease.

Discordance exists in the literature about the possible relationship of PROL and symptomatology in schizophrenia. Some studies have demonstrated significant associations between plasma PROL levels and severity of clinical symptoms in patients with schizophrenia on antipsychotic medication (Newcomer et al., 1992) and also for those who were not on medication (Kleinman et al., 1982, Ferrier et al., 1984). However, Otani et al. (1996) found no association between PROL concentration and psychopathology scores in a group of 56 (28 men, 28 women) unmedicated patients with schizophrenia. Appleberg et al. (2000) found a correlation between clinical scales assessing hallucination and serum PROL levels in 17 drug-free patients with non-affective psychoses.

2.3.2 Relationship Between Cortisol (CORT) and Symptomatology in Schizophrenia

Examination of the role cortisol in schizophrenia has resulted in inconsistent findings. Patients with schizophrenia are reported to be impaired in their biological response to stress by demonstrating a blunted CORT response to psychosocial stress. It is hypothesised that this reflects cognitive dysfunction, based on biological dysfunction in the brain structures that are responsible for these processes, i.e. the PFC and the limbic

system (amygdala-hippocampus complex; Gispen-de Weid, 2000). In particular, it is suggested that dysregulation of CORT may reflect hippocampal abnormalities and memory deficits associated with psychosis (Walder et al., 2000). The stimulation of glucocorticoid receptors in the hippocampus contributes to a negative feedback system that dampens HPA activity. McEwen (1998) suggested that if a stress stimulus is not appropriately responded to, for example when the HPA system is hyper- or hypo-responsive, or not able to habituate, stress may enhance disease susceptibility. Such dysfunction in the HPA system is less clear in schizophrenia, and its involvement in the actual onset of the disorder is unclear and only reported in a minority of patients (Gruen and Baron, 1984). Hypercortisolemia has been reported in patients with schizophrenia (Gil-Ad et al., 1986; Whalley et al., 1989).

Some studies have also suggested a significant relationship between HPA activity and symptomatology in schizophrenia. It has been suggested that the association between CORT levels and symptomatology is a result of the augmenting effects of CORT on dopamine activity (Walker and Diforio, 1997). In some studies CORT levels have been associated with higher positive symptoms (Kaneko et al., 1992; Rybakowski et al., 1991), whereas in others it is related to severe negative symptoms (Newcomer et al., 1991; Tandon et al., 1991). Walder et al. (2000) reported that CORT levels were positively correlated with ratings of positive, disorganised, and overall symptom severity, but not with negative symptoms. Kaneko et al. (1992) found that 20 of 34 patients with chronic schizophrenia, taking conventional medication, exhibited an abnormal diurnal variation of salivary CORT levels. These patients also scored higher on negative symptom ratings than those with normal CORT levels. In addition, they found that 13 of the 34 patients exhibited abnormal results on the salivary dexamethasone suppression test (DST). Furthermore, these patients with DST non-suppression were more frequently classified into disorganised type, and scored low on anxiety measures compared with patients that showed normal suppression. An earlier study also showed that the majority of non-suppressors in DST among patients with schizophrenia had prominent negative symptoms such as affective flattening, poverty of speech and loss of drive (Coppen et al., 1983). It has been suggested that increased CORT levels in schizophrenia reflect the

depressive symptoms in this disorder or the negative symptom complex (Gispen-de Wied, 2000). Hypercortisolemia would then be interpreted as being related to "mood" or "stress". Several studies have found no differences between patients with schizophrenia and controls in basal CORT levels (Kemali et al., 1985; Roy et al., 1986; Van Cauter et al., 1991; Rao et al., 1995). The use of conventional antipsychotics in these studies should be taken into consideration when interpreting these findings, as acute administration of conventional antipsychotics decreases plasma levels of CORT, due to their anticholinergic activity (Meltzer, 1989; Wik, 1995). However, chronic use of conventional treatment appears to restore this initial decrease, as under these circumstances, unaltered CORT levels are found (Meador-Woodruff and Greden, 1988). Normal CORT levels have been reported to be found in both medicated and unmedicated patients (Rao et al., 1995) further confusing the issue of medication influences.

2.3.3 Role of Progesterone in Schizophrenia

Little attention has been given to the role of PROG in psychiatric disorders, even though it has been suggested that a sudden drop in progesterone levels may contribute to the development of such disorders. Primarily, the focus has been on measuring progesterone levels in menstrual cycle studies, studies of HRT or in studies of female patient populations with abnormal levels of this hormone (e.g. in CAH and Turners syndrome). Within psychiatric literature, it has been suggested that variations in the secretion patterns of PROG may contribute to the development of mental illness, in particular dysphoric mood states in the postpartum period. (Harris et al., 1994, Brockington and Meakin, 1994).

Several studies have reported that PROG has psychotropic properties in various mammalian species (Kavaliers and Wiebe, 1987, Bitran et al., 1995, Lancell et al., 1996) and in humans (Bäckström et al., 1984, Friess et al., 1997) after intravenous or oral administration. Wetzel et al. (1998) has offered explanatory models in that P may be acting as a functional antagonist at the 5-HT_3 receptor.

2.4 Gonadal Hormones and Neurocognitive Function in Schizophrenia

The above review (see neurocognitive deficits in schizophrenia) points to women exhibiting the tendency to be less vulnerable to particular cognitive deficits, especially those involving verbal processing, when compared to schizophrenic men. Lewine et al.'s (1997) finding that women with an earlier onset were associated with better neuropsychological performance than women with later onset, generated debate about the role of E serving as a protective factor in the development of schizophrenia in women. The group were to further their hypothesis, suggesting that perhaps the schizophrenia onset age is not affected by Es but rather the point in the females development at which schizophrenia emerges, is influenced by E, in particular the severity of the illness. Amongst women destined to develop schizophrenia, those with earlier onset may be more protected because their onset of illness is closer to their time of peak E levels (during their early 20`s) than in women with later onset of illness.

Few studies have looked at the possible relationship of hormones to cognition in schizophrenia. A recent study by Hoff et al. (2001) examined the relationship of E and PROG levels with psychiatric symptoms and neurocognitive performance in a group of 22 women with schizophrenia. They found that average E levels from four consecutive weekly blood samples were positively related to measures of global cognitive function, verbal and spatial declarative memory, and perceptual motor speed. However no relationship was found between E or progesterone levels and psychiatric symptoms. These findings supported the notion that higher E levels were associated with better cognitive ability and with reference to Hoff et al.'s study; this was now extendable to female patients with schizophrenia. However, a possible confounding factor in this study was that the 22 female patients were not similar in E profile, namely: 3 were taking oral contraceptives, 7 were receiving ERT, and 12 were receiving neither.

Based on findings of better performance on spatial tasks during the low E phase, and better verbal abilities during the high E phase of the menstrual cycle, Thompson et al.,

(2000) tested a group of 31 premenstrual normal control subjects and 29 women with psychosis on a cognitive battery over the menstrual cycle. Subjects were tested twice, once during the follicular phase (low E) and once during the luteal phase (high E) of the cycle. They found no difference between the groups on the Positive and Negative Symptom Scale scores (PANSS) between the follicular and luteal phases of the menstrual cycle. They found that both a normal group of women, and a group of women with psychosis performed better on the revised mental rotation test and the Trails A during the follicular phase of the menstrual cycle. However, contrary to findings from normative studies, during the high E phase, control women demonstrated no improvement on verbal-articulatory-motor tasks, and females with schizophrenia performed worse on the Purdue pegboard. The authors hypothesised that the adverse effect of high levels of E on motor performance in females with psychosis could be due to the confounding influence of their disease process and medication.

2.4.1 CORT and Cognition in Schizophrenia

Consistent with the theory that the hippocampal system plays a role in declarative memory (Squire, 1987, 1992), a relationship between hippocampal morphology and memory has been established in studies of non-schizophrenic subjects, in that the volume of the hippocampus is inversely correlated with memory test performance (Starkman et al., 1992; Lencz et al., 1992). Few studies in schizophrenia spectrum patients, have failed to demonstrate a relationship between delayed memory and hippocampal volume (Colombo et al., 1993; DeLisi et al., 1991; Torres et al., 1997).

Dysregulation of the HPA axis has also been related to cognitive deficits in schizophrenia. An inverse association between CORT levels and performance on measures of hippocampal function (particularly declarative memory) in healthy subjects has been found. This has been demonstrated in: (1) studies where levels of glucocorticoids are experimentally manipulated and result in deficits on memory tests· (Kirschbaum et al., 1996; Newcomer et al., 1994; 1999) (2) studies in which stress-induced alterations in CORT levels are associated with memory deficits (Lupien et al.,

1997), and (3) longitudinal studies of the relation between age-related declines in CORT and memory performance (Seeman et al., 1997). Walder et al. (2000) argue that the precise nature of memory deficits following acute elevations in CORT is however unclear. Some studies suggest impairments in immediate recall following stress-induced CORT secretion (Lupien et al. 1997). On the other hand, other studies suggest retrieval specific impairments following exogenous corticosteroid treatment (De Quervain et al., 2000).

There is limited literature on the role of CORT in cognition in schizophrenia. CORT appears to have differential effects on aspects of cognitive functioning, although the nature of its relationship to cognition in this patient group has yet to be consistently defined. One study reported inverse relationships between early morning (8.00a.m) postdexamethasone CORT levels and auditory verbal learning deficits in unmedicated schizophrenic subjects (Newcomber et al., 1991) In another study by the same author (Newcomer et al., 1998) the effects of dexamethasone versus placebo on verbal memory performance in patients with schizophrenia over 4 days were investigated. Their findings demonstrated higher plasma CORT concentrations (before dexamethasone treatment) and reduced performance on memory and frontal lobe tasks in medicated schizophrenic males and females. Walder et al. (2000) examined CORT levels and psychotic symptoms in 18 patients with schizophrenia (or schizoaffective disorder), 7 with a nonpsychiatric disorder and 15 normal control subjects, and also tested them on measures of memory and executive functions. They found that patients with psychotic disorder demonstrated poorer performance on the cognitive measures compared with the normal comparison group, and that performances on all tests were inversely correlated with CORT levels in all the subjects.

2.5 Lateralization in Schizophrenia

Neuropsychological, neuroanatomic and neurophysiological studies demonstrate that impairment in schizophrenia appears to be predominantly dependent on functions that rely on the left hemisphere (Sakuma et al., 1996; Gur and Chin, 1999). Some previous

research has found evidence of "hypolateralisation", that is, typical onset men (first hospital admission before 25 years old) and women (first admission after 25 years old) may exhibit less lateralization of behavioural function than atypical onset men and women (Lewine et al., 1997; Scheller and Lewine, 1999). In a study by Lewine et al. (1996), female patients demonstrated greater right than left hemisphere impairment than male patients, who were equally impaired in both hemispheres. A follow up IQ study by Purcell et al. (1998) found that male patients, in comparison to female patients, more frequently exhibited greater discrepancies in verbal IQ than in performance IQ (>15 points). The `verbal IQ > performance IQ discrepancies` seen in this study and other studies (Cullari, 1985; Pernicano, 1986; Page, Steffy, 1984) appear less consistent with the left hemisphere dysfunction theory of schizophrenia.

Indices of functional laterality can also be acquired by contrasting the performance on tasks mediated by networks related to left and right hemispheric processing. Ragland et al. (1999) examined laterality indices across motor, sensory, language versus spatial and verbal memory versus spatial memory domains in a group of 75 patients with schizophrenia (45 men, 30 women) and 75 demographically matched controls. The results demonstrated that patients showed deficits across tasks compared to controls, and the extent of laterality varied by domain. Patients were more impaired in language (a function known to be more dependent on the left hemisphere) than in spatial domains, which suggests a probable left hemisphere dysfunction. Male patients showed superior performance in spatial tasks relative to performance in language tasks, whereas female patients performed the same on both domains.

Primarily, contralateral pathways control the left and right sides of the body. Tasks that measure motor and sensory abilities can provide a direct measure of functional asymmetry. Studies have had a tendency to use handedness as an indicator of motor asymmetry. However, a growing body of literature suggests that hand preference itself is a continuous rather than dichotomous variable (Dean and Reynolds, 1997) and that simple handedness questionnaires therefore do not provide a reliable indicator of disrupted hemispheric laterality in schizophrenia (Torrey et al., 1993).

It has also been suggested that schizophrenic patients are more often left- or mixed-handed compared to healthy subjects and non-schizophrenic psychiatric patients (Sommer et al., 2001). Some studies have found that left handedness and crossed dominance have been associated with early onset of illness (Piran et al., 1982); inferior social competence (Merrin, 1984), more negative symptomatology (Andreasen et al., 1982), increased ventricle-brain ratios and poor performance on neuropsychological tests (Katsanis and Iacono, 1989). Lewine et al. (1989) found a correlation between clinical anomalies, reversed visual field preference, and MRI abnormalities in males with schizophrenia. The data support the hypothesis that 'pathological' left sided handedness and eye preference may be associated clinically to a severe form of the illness to which males are more prone as a result of neurodevelopment insults in early life (Murray, 1991). In addition, a causal relationship between schizophrenia and decreased cerebral lateralisation was reported in a study by Crow et al. (1996). This group found that children of mixed hand preference were more likely to develop schizophrenia in later life.

Measures that assess fine motor speed such as the finger-tapping test (Reitan and Wolfson, 1985) might provide another index of motor laterality. Although there is evidence of general bilateral slowing, speed advantages for the dominant hand tend to be preserved in schizophrenia, suggesting normal patterns of cerebral dominance (Ragland et al., 1999). Furthermore, medication effects can confound the results. Thus, it would appear that motor indices do not provide optimal measurements of abnormal patterns of cerebral dominance in patients with schizophrenia. Sensory measures can nevertheless provide convincing evidence of laterality. Studies which have used auditory dichotic listening tasks (Lishman et al., 1978; Wexler et al., 1991; Ragland et al., 1992) and visual tachistoscopic tasks (e.g. Gur 1978) show reductions in the normal right ear or right hemifield advantages for verbal stimuli, which supports models of abnormal left hemisphere function in schizophrenia.

Measures that assess memory and attention provide a less direct measure of hemispheric laterality because these functions do not have clear contralateral representations. The most conclusive laterality differences for these functions have been obtained with visual attention tasks. In tests of directed attention, patients with schizophrenia show subtle impairments in the right visual field, indicative of left hemisphere dysfunction (Posner et al., 1988; Wigal et al., 1991).

Patients with schizophrenia perform poorly on most cognitive tests; this is independent of medication. There is evidence of more severe impairment of memory, attention and executive functioning. The differential cognitive deficits are further supported by structural and functional brain imaging studies. Ragland et al. (1999) demonstrated greater impairment of functions, controlled by the fronto-temporal brain regions, without clear evidence of laterality effects. The group suggested that it was unclear whether sex differences in cognitive function and hemispheric organisation interact with sex differences in schizophrenia. Lewine et al. (1996) compared the performance of male and female patients with schizophrenia to a group of healthy control men and women. Contrary to previous studies, they found female patients performed worse than male patients on verbal and spatial memory and on visual processing tasks. Although male patients were equally impaired on functions mediated by left and right hemispheres, female patients performed relatively worse on right hemisphere tasks. The authors concluded that schizophrenia in women might be partially understood as a right hemisphere dysfunction. However, in this study almost half of the female patient sample had a diagnosis of schizoaffective disorder, and because affective illness has been associated with right hemisphere dysfunction (Banich et al., 1992), it is not clear whether this influenced the study as a confounder.

Several studies have examined the cerebral asymmetry of cognitive functioning using MRI in patients with schizophrenia. The literature has shown a consistent relationship between neurocognitive impairment with ventricular enlargement and sulcul widening (Johnstone et al., 1976; Donnelly et al., 1980; Golden et al., 1982; Kemali et al., 1985; Pandurangi, 1986). DeLisi et al. (1991) reported greater lateral ventricular size,

particularly on the left side in chronic and first episode patients compared to controls, and also reported that ventricular size was greater in chronic patients compared to first episode patients with schizophrenia. Using MRI, Hoff et al. (1992) investigated areas of the brain associated with language functioning. They examined cognitive functioning and differences in measurements of the length of the lateral sulcus and borders of the planum temporale. A group of first episode schizophreniform (patients who have been ill for less than 6 months) patients and control subjects were compared. The patients demonstrated a diffuse pattern of neuropsychological impairment compared with controls. Furthermore, an atypical pattern of anatomic lateral asymmetry was found in the female patients, with females demonstrating a reduction in the usual left greater than right length of the lateral sulcus. This atypical asymmetry in the lateral sulcus was associated with better cognitive function, particularly in patients. The authors suggested that atypical lateralisation in an area critical to language function may be related to cognitive functioning.

2.6 Structural Brain Abnormalities

Non-invasive techniques used to investigate the neural morphometry of patients with schizophrenia have been conducted using computerised tomography and MRI scans. The most robust finding from studies of CT scans is that patients with schizophrenia tend to have increased ventricle-brain ratios compared with normal people (Shelton and Weinberger, 1986). Such changes are reported to be non-progressive, present at the onset of illness, and are associated with poor premorbid function (Pearlson et al., 1985; Nasrallah et al., 1986; Turner et al., 1986).

MRI studies have shown smaller temporal lobe structures in patients with schizophrenia (Johnsone et al., 1989a; Suddath et al., 1990). Post-mortem studies of the brains of patients with schizophrenia show abnormalities in the hippocampal region (Bogerts et al.; 1985; Brown et al., 1986; Jacob and Beckmann, 1986). Additionally, studies have found that no gliosis accompanies these lesions, which suggests that these abnormalities may originate *in utero* or in early infancy, possibly through genetically-mediated arrest of cell migration or pre- and peri- natal environmental insults (Jacob and Beckman, 1986;

Lewis, 1989; Gill et al. 1989). A more recent study by Job et al. (2002) compared structural MR images of the brain in first-episode patients with schizophrenia compared to normal control subjects, using automated voxel based morphometry. The findings demonstrated significant decreases in grey matter in the schizophrenia patients relative to the control group in the right anterior cingulate, right medial frontal lobe, left middle temporal gyrus, left postcentral gyrus and the left limbic lobe. When restricting the analysis to the amygdala-hippocampal complex, schizophrenic patients exhibited grey matter decreases in the left and right uncus, parahippocampal gyri, and the right amygdala.

Several studies have investigated sex differences in brain morphology in patients with schizophrenia. Crow (1985) and Pearlson`s group (1989) reported sex differences in male patients are associated with earlier onset of the disorder, poorer premorbid adjustment, more negative symptoms, more maternal obstetric complications and poorer response to treatment. They also found that male patients with this illness had more severe brain abnormalities, particularly ventricular enlargement. A conclusion from this could be that male patients present a more severe form of the illness compared to women, and this may be reflected in more structural brain abnormalities.

Some MRI and CT studies have further supported this. In agreement to this, Andreasen et al. (1994), Lieberman et al. (1992), and Haas et al. (1991) having examined sex differences in brain morphology, found larger ventricles in male patients. Other studies have demonstrated that female patients have larger ventricles compared to female controls, while male patients do not show a difference relative to comparison subjects (Gur et al., 1991; Andreasen et al., 1982; Gur et al., 1994; Nasrallah et al., 1990). A large MRI study examining general and regional brain morphology found no sex differences in men and women with schizophrenia and control subjects. Some studies have reported men to exhibit more abnormalities than women in sulcal cerebrospinal fluid (CSF; Vita et al., 1988; Gur et al., 1991), total brain tissue (Andreasen et al., 1994), anterior temporal horn area (Johnstone et al., 1989; Bogerts et al., 1990), temporal lobe volume (Cowell et al., 1996), smaller medial temporal volume (e.g. hippocampus and amygdala;

Bogerts et al., 1990; Gur et al., 2000) and superior temporal gyrus (Gur et al., 2000; Reite et al., 1997). In addition, more left lateralized abnormalities among men have been reported, such as smaller volumes of the left planum temporale (Hirayasu et al., 2000; Kwon et al., 1999; Rossi et al., 1991), left Heschl's gyrus (Hirayasu et al., 2000), left superior temporal gyrus (Falkai et al., 1995) and left hippocampus (Shenton et al., 1992). Conversely, studies have also reported females to have more abnormalities than males, particularly in frontal lobes (Nasrallah et al., 1990) and the corpus callosum (Hoff et al., 1994). In a study of first episode patients with schizophrenia, Hoff et al. (1994) observed that female patients had a smaller total corpus callosum area than female controls, with no difference between male patients and controls.

More specifically, studies have reported smaller volumes of the heteromodal association areas amongst women with schizophrenia, for example in the dorsalateral prefrontal cortex and the superior temporal gyrus (Schlaepfer et al., 1994) and orbital prefrontal cortex (Gur et al., 2000). Gur`s group (2000) also found similar abnormalities in the dorsolateral prefrontal cortex in females. Nopoulos et al. (1997) examined sex differences in brain morphology using MRI in a group of eighty patients with schizophrenia (40 men, 40 women) and eighty controls matched by age and sex. They found that male patients had larger ventricles compared to the male comparison group, but female patients showed no significant difference in comparison with healthy female subjects. In a more recent MRI study, Goldstein et al. (2002) investigated the impact of normal sexual dimorphisms on sex differences in structural brain abnormalities in schizophrenia. The group examined 40 patients with schizophrenia compared with 48 matched normal comparison subjects. The results showed normal patterns of sexual dimorphisms were disrupted in schizophrenia. Sex specific effects were primarily evident in the cortex, particularly in the frontomedial cortex, basal forebrain, cingulate and paracingulate gyri, posterior supramarginal gyrus and planum temporale. Normal asymmetry of the planum was also disrupted in men and women with schizophrenia. Hajek et al. (1997) detected bilateral volume reduction of the grey matter of the posterior superior temporal gyrus (greater on the left), in schizophrenic males. However, a post-mortem study by Vogeley et al. (1998) did not find any sex differences in total superior

temporal gyrus volumes, although they reported that female patients had significantly reduced volume and length of the middle section of the left superior temporal gyrus compared to male patients. Conversely, Rojas et al. (1997) reported that male patients, but not female patients, had reduced Heschl's gyri. Bryant et al. (1999) reported smaller left temporal lobe volumes in male patients compared to male controls, though no such difference was found in the comparison of female patients with controls.

The corpus callosum is known to play an important role in the integration of cerebral activity between the two hemispheres (Trevarthen, 1990). Studies of the corpus callosum reveal abnormalities in patients with schizophrenia of both sexes, with no obvious pattern of abnormality, but methodological issues have complicated the studies. Nasrallah et al. (1986) found significantly increased thickness of the anterior and middle, but not posterior, parts of the corpus callosum in schizophrenic compared to normal females on MRI. There were, however, no differences between schizophrenic and normal men. In contrast, Hauser et al. (1989) found that schizophrenic women had reduced thickness of the anterior callosum compared to female controls in MRI studies. Raine et al. (1990) observed on MRI that normal men had a thicker callosum than normal women; however, this sex difference was reversed in schizophrenic patients, with female patients having a thicker callosum than male patients. Lewine et al. (1990) found a higher proportion of schizophrenic men had very small corpus callosum areas and Woodruff et al. (1993) reported the corpus callosum area, particularly the middle part, was reduced in schizophrenic men only. Scheller-Gilkey and Lewine (1999) found that typical onset women (first hospital admission after age 25) had larger corpus callosum compared with typical onset men, atypical onset men, and women.

In summary, studies examining structural abnormalities in schizophrenia have been limited by a number of methodological problems, including inadequate sample sizes, over-representation of men, sampling from chronically ill population with biases towards females with more severe illness, and variability in the size, structures and general population of both sexes. There have also been procedural problems in measurement, namely thickness and spacing of slices, differences in measurement procedures amongst

research centres (use of different boundary definitions) with failure to control for age, hand preference, weight, height and possibly education level. Despite these methodological issues, there is important evidence of sex difference with respect to brain abnormalities, which seems to indicate that males exhibit more abnormalities than females.

2.7 Neural Correlates of Cognitive Functions in Schizophrenia

Neuropsychological performance in patients with schizophrenia is generally associated with regional brain dysfunction. Brain imaging and neuropsychological studies have demonstrated deficits in frontal functioning in patients with schizophrenia. These deficits appear on tests such as verbal memory, verbal abilities, executive functioning and spatial working memory (which are thought to represent frontal brain functioning). In the schizophrenia literature, it has been consistently found that attenuation in frontal activity in patients with schizophrenia is associated with performance on these aforementioned tasks. (Curtis et al., 1998; Weinberger et al., 1996, 1992; Weinberger and Berman, 1996).

2.7.1 Neural Correlates of Verbal Abilities in Schizophrenia

As described in Chapter 1, verbal fluency is associated with predominantly left frontal functioning. This has also been demonstrated in lesion studies and fMRI investigations (Peret, 1974; Miceli et al., 1980; Schlosser et al., 1998). PET studies have investigated CBF changes during verbal fluency tasks in patients with schizophrenia. Studies which have tested acutely ill, drug-free (Grasby et al., 1994), and chronically ill patients, have suggested that patients with schizophrenia exhibit abnormally correlated regional CBF changes in frontal and temporal regions compared with control subjects. More specifically, when scanned under identical conditions, patients with schizophrenia have shown small, positive frontotemporal correlations in rCBF, compared to relatively large negative correlations in control subjects.

Some studies have shown that during verbal cued recall tasks, patients with schizophrenia tend to demonstrate deficits in cingulate cortex (Dolan et al., 1995) and deficits in frontal-temporal activity relationships (Friston et al., 1996). These findings support the hypothesis that frontotemporal dysconnectivity may be a central pathophysiological feature of schizophrenia (McGuire and Frith, 1996). Although these studies implicate the role of dysfunctional left frontal areas as being a key abnormality in schizophrenia, Sommer et al. (2001) argue that previous studies have not addressed whether the reduced lateralization in schizophrenia is the result of decreased language activity of the left hemisphere, or whether it is the consequence of increased language-related activity in the right hemisphere. In an attempt to address this point, Sommer et al. (2001), using fMRI, examined hemisphere dominance for language processing in 12 patients with schizophrenia and 12 healthy controls, during performance on a verb generation and a semantic decision task. They found that language processing was less lateralized in patients than in controls, and this was due to increased activation in the right hemisphere of the patients. They also found no evidence of reduced activity in the left hemisphere in patients. Further analysis revealed that the decreased language lateralization was associated with more severe hallucinations. The authors suggested that decreased lateralization in patients may be a result of a failure to inhibit the right hemisphere.

Few fMRI studies have examined the neural correlates of verbal fluency in patients with schizophrenia. Curtis et al. (1998) conducted an fMRI study to elucidate neural activation in 5 patients with schizophrenia and 5 matched controls whilst performing a covert verbal fluency task. In this task subjects were instructed to silently generate words beginning with an aurally presented cue letter. This task alternated with paced silent repetition with the aurally presented word "rest". They found significantly reduced power of response in the left dorsal PFC, the inferior frontal gyrus, and the insula, but significantly increased activation in the medial parietal cortex in the schizophrenic patients. However, the control subjects showed increased activation in the left PFC, the insula bilaterally, the midline supplementary motor area, and the medial parietal cortex.

In order to further explore the idea of hypofrontality in schizophrenia, Curtis et al. (1999) examined the neural correlates of two covert tasks; verbal fluency and a semantic decision task in 5 male schizophrenic and 5 controls matched on demographic variables. In the semantic decision task, subjects were asked to decide whether a visually presented cue word was 'living or non-living' and to silently articulate the response. They found that patients exhibited a significant reduced power of response in some prefrontal regions during the verbal fluency task relative to control subjects, though the same was not found for the semantic decision task; whereas, in the control group, both tasks were associated with activation of PFC. The significant group x task interaction identified areas in the left inferior frontal gyrus, left dorsolateral PFC and the supplementary motor areas. The results of this study suggest that hypofrontality or reduced frontal activation is not a fixed deficit, but that it depends on the specific cognitive demands of the task used. In support of this, Yergelun-Todd et al. (1996) reported decreased left prefrontal cortical activation and greater left temporal activation in patients with 12 patients with schizophrenia compared to 11 healthy subjects during a verbal fluency task.

2.7.2 Neural Correlates of Spatial Cognition

2.7.2.1 Neural Correlates of Working Memory

Neuropsychological studies have consistently demonstrated impairments in working memory functions in schizophrenia. The ability to temporarily maintain and manipulate information on-line is the basis of working memory. As described in Chapter 1, the PFC is the brain region that is commonly associated with working memory. Dysfunction in the PFC (hypofrontality) has been consistently implicated in schizophrenia and has been linked to deficits in working memory function (Goldman-Rakic, 1991; Carter et al., 1996; Servan-Schreiber, 1996).

Several studies have supported a link between PFC and working memory disturbances, (e.g. Malmo, 1974; Cornblatt and Keilp, 1994; Abramcyk et al., 1983; Park and Holtzman, 1992; Buchsbaum et al.., 1992; Weinberger et al., 1980; Callicott et al., 1998;

Berman et al., 1986; Andreasen et al., 1992; Monach et al., 2000). More specifically, working memory deficits in schizophrenia have generally been associated with the DLPFC in studies that have employed the N-Back working memory task. In an fMRI study, Callicott et al. (1998) examined brain activity in 10 inpatients with schizophrenia and 10 control subjects whilst performing a N-Back working memory task. In contrast to normal subjects, they found patients with schizophrenia failed to activate the DLPFC. Callicott (1997) suggests that patients are able to activate the PFC at lower levels of working memory (i.e. one-back), but may have reduced capacity compared with healthy controls to activate PFC in response at higher loads (i.e. two-back). Carter et al. (1998) reported similar findings to those of Callicott et al. (1998), using PET in a group of 8 patients with schizophrenia and 8 matched controls. They found that under low working memory load conditions, the accuracy of both groups on the N-Back task was equal, but when the memory load increased, the patient's performance deteriorated relative to the comparison subject's performance. The rCBF response to increased working memory load was significantly reduced in the patients' right DLPFC. Weinberger et al. (1996) also found reduced prefrontal activation during the N-Back task in patients with schizophrenia even when performance was normal. This was further replicated in an rCBF study (Weinberger and Berman, 1996).

The above observations, which suggest that hypofrontality appears to be evident in the context of capacity limitations, have been confirmed by recent studies in healthy subjects. A PET study by Goldberg et al. (1998), showed that during performance on a dual task paradigm, healthy subjects became relatively `hypofrontal` when pushed beyond their capacity to maintain accuracy. This hypofrontal response was further observed in another study using a word-recall task of increasing word-list length in a group of healthy subjects (Grasby et al., 1994). Similarly, Callicott et al. (1999) demonstrated an inverted-U shaped PFC response to parametrically increasing working memory difficulty in healthy subjects, who became relatively hypofrontal as they were pushed beyond their working memory capacity.

Thus it appears that, under certain circumstances, hypofrontality can be a normal physiological response to excessive load. However, these findings make it difficult to reconcile whether hypofrontality as a 'finding' in schizophrenic patients is a direct (i.e. disease dependent) representation of PFC pathology, or whether hypofrontality simply reflects diminished behavioural capacity that might occur for any subject pushed beyond capacity (i.e. disease independent; Callicott et al., 2000). For example, Fletcher et al. (1998) administered a parametric word list recall task to patients with schizophrenia, and found that hypofrontality occurred only in the context of list lengths beyond the patients' memory capacity. These findings suggested that patients with limited working memory capacity might be expected to become hypofrontal when studied beyond their working memory capacity. In another fMRI study, Callicott et al. (2000) examined performance on a parametric N-Back working memory task in a group of patients with schizophrenia (N = 37) and a healthy control group (N = 32). In patients that performed relatively well on the task, three major deviations from the 'healthy' pattern of PFC fMRI activation to varying working memory difficulty were found. Firstly, the authors observed a greater magnitude of PFC activation in the context of slightly impaired working memory performance (which is termed physiological inefficiency). Secondly, the significant correlation between behavioural working memory performance and dorsal PFC activation were in opposite directions in both the groups. Thirdly, the magnitude of the abnormal dorsal PFC response was predicted by an assay of N-acetylasparate (NAA) in dorsal PFC, a measure of neuronal pathology (obtained using proton magnetic resonance spectroscopy). Patients had significantly lower dorsal PFC (NAA) than the control group, and dorsal PFC NAA inversely predicted the fMRI response in dorsal PFC to varying working memory difficulty. This finding supported the theory that abnormal PFC responses arise from abnormal PFC neurons.

In summary, the data proposes that performance on the N-Back working memory task is dependent on brain areas within the PFC, in particular the DLPFC. In addition, the notion of hypofrontality appears to be demonstrated in both patients and healthy controls who are pushed beyond the capacity to maintain accuracy, or when the demands of the task become too difficult to be able to maintain optimal performance.

Generally, neuroimaging studies have restricted the studies to tasks that activate specific brain areas that are known to show some abnormality in schizophrenia, such as executive functioning, on particular tasks such as the N-Back working memory task. With regard to sexually dimorphic cognitive tasks such as mental rotation, there have not been any studies that have looked at neural activation in patients with schizophrenia during performance on these tasks, in either males or females

2.7.3 Neural Correlates of Cognitive Inhibition

Reduced prefrontal activation has also been reported in patients with schizophrenia during performance on tasks that measure inhibitory functions. Rubia et al. (2001), in an fMRI study, examined neural activation to the 'stop' and 'go-no-go' motor inhibition tasks in 6 medicated male schizophrenics and 7 healthy comparison subjects matched for sex, age and education. There were no group differences in performance but the patients demonstrated reduced BOLD signal response in left anterior cingulate during both tasks. The authors also found that the patient group demonstrated reduced left rostral dorsolateral prefrontal, increased thalamus and putamen BOLD signal responses during performance on the 'stop' task. There has been no study to date that has examined the neural correlates of the Stroop test or forward backward counting in patients with schizophrenia.

Chapter 3

Study 1: The Relationship of Circulating Gonadal hormones and Gonadotropins to Within-Sex Differences in Cognitive Performance

3.1 Summary

This study examined differences between a sample of healthy men (n = 42) and women (n = 42) aged 18-35 years during with performance on a sexually dimorphic cognitive battery and examined associations between organisational influences of endogenous levels of gonadal hormones and gonadotropins and cognitive performance between the sexes. Serum blood samples (10ml) were collected between 0900 and 1030, and concentrations of testosterone (T), estradiol (E), progesterone (PROG), luteinizing hormone (LH), follicle-stimulating hormone (FSH) and sex hormone binding globulin (SHBG) were measured. Participants also completed three spatial tasks (mental rotation, modified judgement of line orientation and computerized Benton judgement of line orientation), two verbal tasks (letter and category fluency), an inhibition task, a working memory task, and a control measure (vocabulary test). Results demonstrated significant sex differences favouring men on all the spatial tasks and the inhibition task, and differences favouring women on the category fluency task. There were sex differences on specific conditions of the working memory task, some favouring men and some women, and no sex difference on the vocabulary test. The only significant relationships between hormones and cognitive performance were not predicted, and involved specific conditions of the spatial and inhibition tasks and PROG, LH, FSH or SHBG. These results suggest there are few if any consistent and substantial relationships between endogenous levels of gonadal hormones or gonadotropins and these cognitive abilities in men or women.

3.2 Introduction

Sex differences in cognitive abilities are well documented. Typically men outperform women on those spatial tasks requiring transformations in visuo-spatial working memory, such as mentally rotating and matching three-dimensional objects (Hyde and Linn, 1988; Halpern, 1992; Voyer et al., 1995). Women score higher than men, on average, on tests of verbal fluency and synonym generation (Hines, 1990; Halpern, 1992), both of which require speedy retrieval and accurate production of words based on phonetic and semantic recognition (Loring-Meier and Halpern, 1999).

The relationships between hormones in adulthood and sex dimorphic cognitive abilities are far from clear. Several factors might have contributed to the inconsistent results that have been previously reported. First, studies have not always used tasks that show sex differences, and the influence of sex-related hormones are expected to be limited to such tasks (Collaer and Hines, 1995). Second, studies have not always measured hormones, relying instead, for instance, on self-reports of menstrual cycle phase, which can be unreliable indices of hormone status (Gordon and Lee, 1993). Third, the time of day when samples were taken often has not been controlled or reported, despite diurnal fluctuations in many hormones (Simoni et al., 1992; Nieschlag and Ismail, 1970; Carlsen et al., 1999). Fourth, studies have often focused on a single hormone, and have not examined other factors that influence the ability of hormones to act, such as SHBG. Fifth, attempts to integrate findings across studies of possible activational influences of hormones have generally not attended to the possibility that results might differ across the three types of situations that have been studied (hormone administration, hormonal fluctuations and single assessments of endogenous hormone levels).

The current study focussed on one approach to studying possible relationships between adult hormone levels and human cognitive performance, by relating endogenous levels of hormones to sexually dimorphic cognitive abilities. In addition, the study controlled for the time of day when samples were obtained and menstrual cycle phase to reduce the impact of these potentially confounding factors. The present study measured five hormones: E, T, P, LH, FSH as well as SHBG, which sequesters T and E and thus limits their ability to act. Cognitive measures were primarily expected to show sex differences

(spatial abilities, verbal fluency, inhibition and working memory) with a task that were not expected to show sex differences (vocabulary) included for control purposes. The main hypotheses tested were based on prior findings and included: 1) men would perform better than women on the spatial tasks (mental rotation, modified judgement of line orientation, MJOLO and computerized Benton judgement of line orientation, BCJOLO), the inhibition and the working memory task, 2) women would perform better than men on letter and category fluency tests, 3) there would be no sex differences on any of the control measures (a working memory task and a vocabulary test, 4) T would correlate positively with performance on tasks at which men excel, and negatively with performance on tasks at which women excel; 5) E would correlate positively with performance on tasks at which women excel and negatively with performance on tasks at which men excel; 6) T would show a curvilinear relationship to performance on spatial tasks; 7) FSH would correlate negatively with performance on spatial tasks in men and women, and positively with verbal fluency in women; and 8) LH would correlate positively with verbal fluency in men and women, and with performance on spatial tasks in men. In addition, the study explored the possibility that SHBG may be involved in relationships between T or E and cognitive performance.

3.3 Method

3.3.1 Participants

Eighty-four healthy volunteers, (forty-two men and forty-two women) aged between 19 and 35 years (men, $M = 28.31$, $SD = 4.81$, women, $M = 27.69$, $SD = 3.96$, $t(82) = .64$, $p = .52$) participated in the study. All participants were recruited by advertisements and posters displayed in the local community and were paid for their participation. All participants reported that they were in good physical health, had never suffered a psychiatric or neurological illness, were not taking psychoactive or hormone medications or substances, were right-handed for writing and were heterosexual. None of the women were currently using oral contraceptives, and all the women were tested between days 3-7 of their menstrual cycles (follicular phase), as determined by self-report and by

measurements of E (M = 159.36, SD = 76.96, normal range = <74-389 pg/ml), P (M = 2.72, SD =1.06, normal range = .60-4.80 ng/ml), LH (M = 6.38, SD =5.51, normal range = 1.4-11.6 mlU/ml) and FSH (m = 6.29, sd =2.79, normal range = 4.1-9.5 mlU/ml). All procedures were approved by the local ethics committee and informed consent was obtained from all participants.

Results for 42 men and 42 women are presented for all tasks, except the mental rotation task where data were available only for 41 men and 42 women (one man did not complete this task).

3.3.2 Procedure and Materials

Because there are circadian variations in hormones, all participants were tested at the same time of day (0900-1030). Venous blood samples were taken (10mls) at the beginning of the test session. One blood sample was taken from each person. Samples were stored at –40 °C. The analysis used for E, P, T, LH and FSH was an Advia Centaur supplied by Bayer Diagostics, Newbury, Berkshire. The technique is a sandwich immunoassay using direct chemiluminesent technology. SHBG was measured using an Immulite analyzer supplied by Diagnostic Products Corporation. The technique is a two-site chemiluminesent enzyme immunometric assay. All hormones were in the normal range for every male and female participant. (See Table 3.1 for summary data). Because serum T and E can be inactivated by binding to SHBG (Vermulen, Verdonck and Kaufman, 1999), we also calculated the concentration of free T in each subject using the equation: Concentration of free T = (6.11-(2.38logSHBG) x 10 x Total T concentration (Wheeler and Nanjee, 1985). General formulae for measuring free E, require measurement of various other parameters including albumin, putting them beyond the scope of the current study.

Immediately following the blood sampling procedure, participants completed a one-hour battery of cognitive tests. Some of the computerized tasks (mental rotation, CBJOLO, inhibition, working memory) were designed for use in a functional magnetic resonance imaging (fMRI) study as well as in the current study.

Table 3.1

Means (standard deviations) and ranges, t and p values for hormones in men and women. The reference ranges for all hormones are based on the ranges provided by the Laboratory at Guy's Hospital

	Men	Women	t-value df= 82	p-value
E(pmol/L)	128.12(55.13) Range: <74 -203	159.36 (76.96) Range: <74-389	-2.13	.03
T(nmol/L)	18.56(5.32) Range: 10-35	1.52(.71) Range:0.5-2.5	20.57	.00
P (nmol/L)	2.92(.99) Range: 1.5-5.3	2.72(1.06) Range: 0.6-4.8	.90	.37
SHBG (nmol/l)	27.67(13.21) Range: 10-62	50.67(27.91) Range: 40-137	-4.82	.00
FSH (IU/L)	3.15(2.66) Range: 1.8 –8.6	6.29(2.79) Range: 4.1-9.5	-5.28	.00
LH (IU/L)	4.80(1.63) Range: 0.7-6	6.38(5.51) Range: 1.4-11.6	-1.77	.08

3.3.3 Cognitive Measures

3.3.3.2 Vocabulary

The vocabulary sub-test of the Weschler Adult Intelligence Scale–Revised (WAIS-R) was used as a measure of general intelligence as well as a control task.

3.3.3.2 Working Memory Task

This computerized test of spatial working memory is a modified version of the working memory task of Callicott et al. (1998). It consists of four conditions (zero-back, one-back, two-back and rest), each presented five times, and each lasting 30 seconds. In each condition a diamond shape is displayed on the computer screen, and in the 0-back, 1-back and 2-back conditions, random single digits are flashed in each corner. Participants are provided with a button box with four buttons, also in the shape of a diamond. In the 0-back condition, participants view the flashing number and respond by pressing the corresponding button on the button box. In the one-back condition participants respond to the location of the number seen one presentation earlier. In the two-back condition participants respond to the location of the number seen two presentations earlier. In the rest condition participants simply view the diamond on the screen. The task lasts 10 minutes, and accuracy and reaction times are recorded by computer.

3.3.4 Spatial Tasks

3.3.4.1 Mental Rotation Test

This computerized three-dimensional task consists of six control and six experimental conditions presented in a randomized order. Each condition lasts 30 seconds and is separated from the next condition by a rest period of 5 seconds, during which time a white cross is displayed on the screen. In every condition, 10 pairs of three-dimensional shapes are presented, and the participant indicates whether the two shapes in each pair are identical or mirror images. In the control conditions, the two shapes are in the same angle of rotation and in the experimental conditions, they are not (see figure 3a and 3b). Images are presented at 10 different angles of rotation, 0° to 180° with half being identical and half mirror images. In total, 120 stimulus pairs are presented to the subject and the task lasts 7 minutes. Participants respond using a button box and accuracy and reaction times are recorded by computer.

3.3.4.2 Computerized Benton Judgment of Line Orientation (CBJOLO)

This computerized version of the BJOLO (Ng et al., 2000) consists of five control and five experimental conditions. Each condition lasts 30 seconds and includes 8 trials of 3.75 seconds each. In total the task lasts 5 minutes. For all trials, participants are asked if the orientation of two lines at the top of the screen matches the orientation of two lines highlighted in an array at the bottom of the screen. For the control conditions, both sets of lines are horizontal. For the experimental condition, the two stimulus lines at the top of the screen are not horizontal and sometimes match the angles highlighted in the bottom array, but sometimes do not (see figure 2). The control condition is always presented first. Participants respond using a button box, and accuracy and reaction times are recorded by computer.

3.3.4.3 Modified Judgement Of Line Orientation (MJOLO)

This test (Collaer and Nelson, 2002) was modified from the BCJOLO to make it more difficult. It was included as well as the CBJOLO to determine if a more difficult task might produce a larger sex difference, and thus a more sensitive measure of hormone effects. There are 20 items in the test. Compared to the BCJOLO, each item includes a larger array of lines at the bottom of the page and shorter lines at the top of the page. Participants are asked to indicate aloud which two angles at the bottom of the page correspond to the two stimulus lines at the top of the page. Response accuracy is recorded.

3.3.5 Verbal Tasks

3.3.5.1 Phonological Fluency

On this measure, participants generate orally, as many words as possible beginning with three specified letters of the alphabet (F, A, S). One minute is allowed for each letter.

The score is the number of words generated, summed over all three letters. Repetitions (repeating the same word) and intrusions (generating a word that does not begin with the specified letter) are also recorded.

3.3.5.2 Category Fluency

On this measure, participants are asked to say aloud as many words as they can think of within three categories (Animals, Fruits and Vegetables). One minute is allowed for each category. The score is the number of words generated, summed over all three categories. Repetitions and intrusions are also recorded.

3.3.6 Inhibition Task

In this computerized task, some trials require participants to respond to obvious stimuli (detecting numbers increasing in numerical order: forward conditions) while others require them to inhibit responses to obvious stimuli in favour of less obvious stimuli (detecting numbers decreasing in numerical order: backward conditions). The task involves 5 forward and 5 backward conditions, each lasting 30 seconds. Between each condition there is a rest period of 5 seconds, during which time a white cross is displayed on the screen. In both conditions, a series of random one and two digit numbers are presented on the screen, one number per second. In the forward conditions 23% of the numbers are presented in the backward direction (F23) and 77% in the forward direction (F77). In the backward conditions 23% of the numbers are presented in the forward direction (B23) and 77% in the backward direction (B77). The task lasts five minutes fifty seconds. Participants respond using a button box to indicate whether the numbers are increasing or decreasing, and accuracy and reaction times are recorded by computer.

All participants completed the tasks in the same order so that no two spatial or verbal tasks followed each other. The order was: vocabulary, mental rotation, phonological fluency, CBJOLO, category fluency, working memory, inhibition, MJOLO.

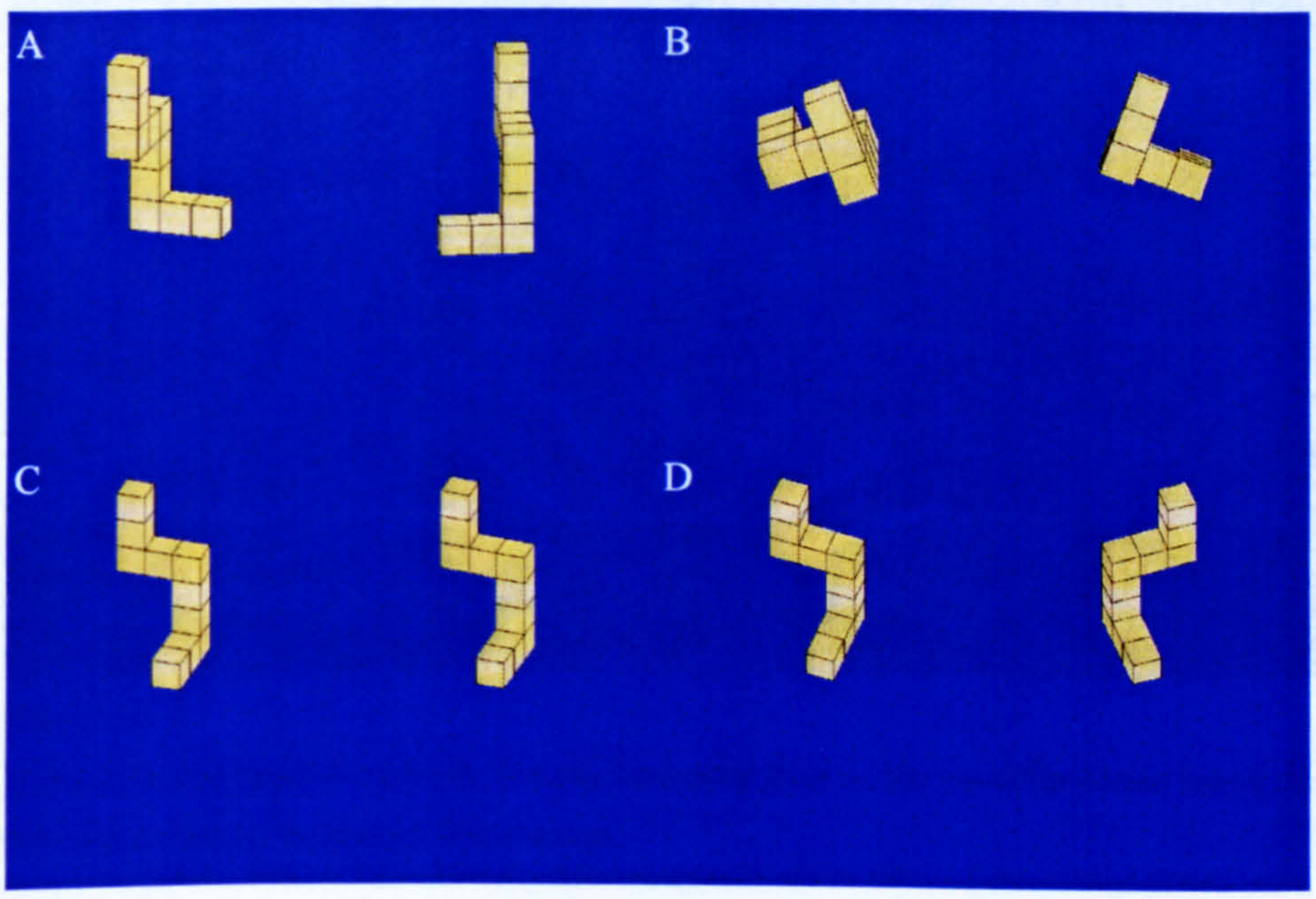

Figure 3.1. The top two images (A and B) are examples of the experimental condition. A: the right hand image is a rotated version of the left-hand image, so the response would be 'same'. B: the right-hand image is a rotated and mirror version of the left hand image, so response would be 'different'. The two images at the bottom C and D are examples of trials in the control conditions. C: the two images are identical (same). D: the two images are mirror versions of one another (different).

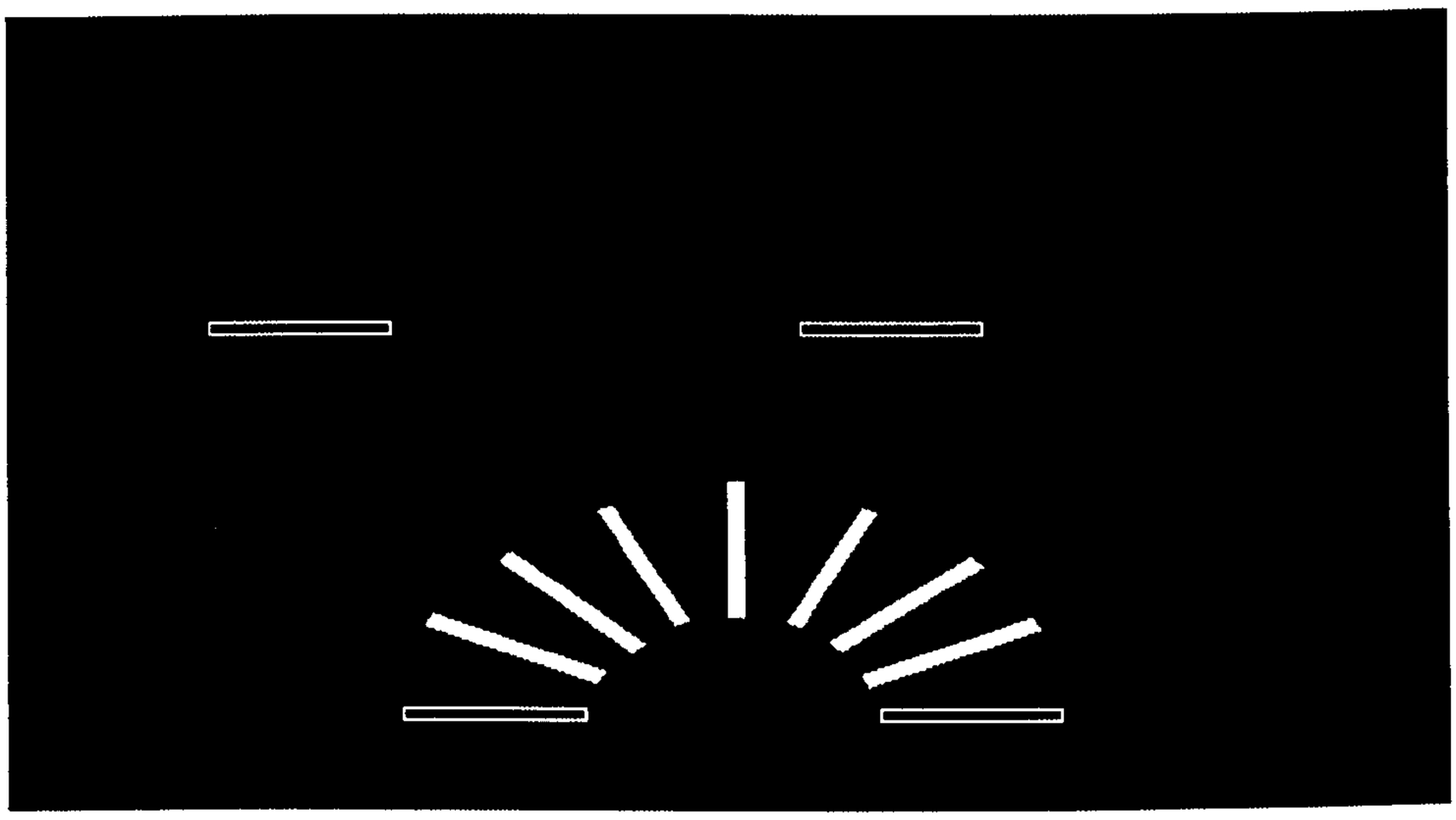

Figure 3.2 a

A trial from the control condition. The two horizontal lines on the top of the screen match the two horizontal lines on the bottom of the screen.

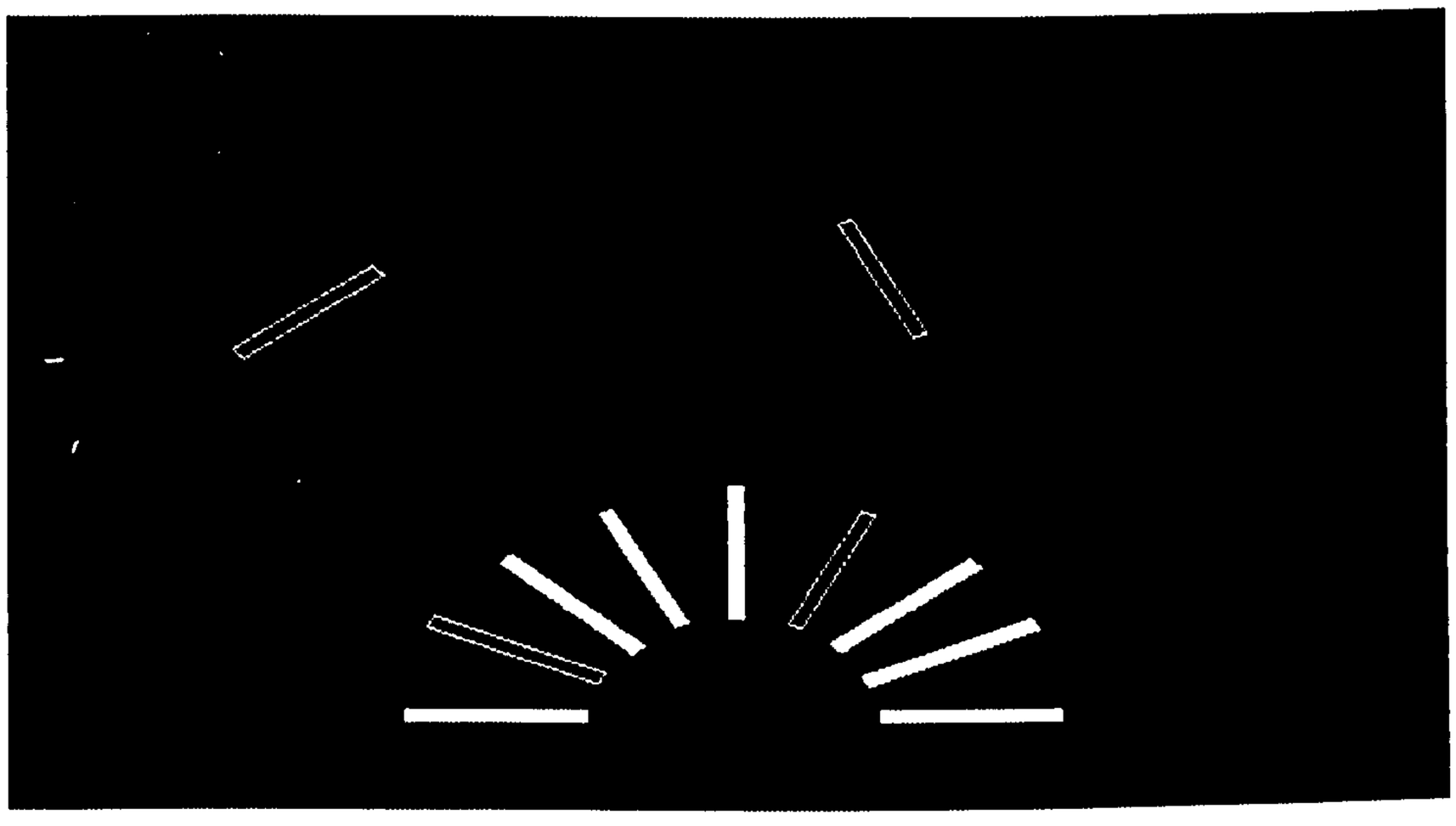

Figure 3.2 bb

A trial from the experimental condition. The two stimulus lines at the top of the screen do not match the two highlighted lines on the bottom half of the screen.

3.4 Statistical analysis

First, ANOVAs were used to determine whether tasks showed the expected sex differences. In most cases, these were one-way (men,women) ANOVAs. For tasks involving different conditions or trial types (mental rotation, inhibition, working memory), two- or three- way ANOVAs were used. Following the ANOVA's, Pearson product-moment correlations assessed associations between task performance and hormones within each sex. In addition, partial correlations were used to investigate relationships between task performance and T and E, controlling for SHBG. Also, the relationship between task performance and levels of free T were investigated.

To test for the hypothesized curvilinear relationship between T and spatial abilities, firstly, quadratic transformations of subjects' deviations from mean T levels were made. Then, a forced entry multiple regression was carried out using the quadratic term as the independent variable, and each spatial task as the dependent variable. This procedure was used to replicate the procedure used in the prior study reporting a curvilinear relationship between T and spatial performance.

3.5 Results

3.5.1 Gender Differences in Task Performance

3.5.1.1 Vocabulary

As expected, there was no sex difference ($F(1,83) = 1.068$; $p = .305$) on the vocabulary test.

3.5.1.2 Mental Rotation

There was a significant sex difference ($F(1,82) = 21.384$, $p < .001$) favouring men for accuracy on the mental rotation task and there was a main effect of condition ($F(1,82) = 715.573$, $p < .001$). There was also a significant two-way interaction between condition and sex ($F(1,82) = 22.637$; $p < .001$) revealing that, as expected, the sex difference was present only in the experimental conditions. There were no significant main effects or interactions for response latency.

3.5.1.3 BCJOLO

There was a sex difference favouring men in accuracy ($F(1,83) = 26.311$; $p < .001$), but not in response latency ($F(1,83) = .098$; $p = .755$) on the BCJOLO. See Table 3.2 for the mean percentage correct for men and women.

3.5.1.4 MJOLO

There was a sex difference favouring men ($F(1,83) = 15.234$; $p < .001$) on MJOLO (only accuracy was assessed). For men, the mean percentage correct for the MJOLO was $M = 75.83$ ($SD = 14.81$), and for women it was, $M = 65.95$ ($SD = 11.43$).

3.5.1.5 Phonological Fluency

There was no sex difference for the number of words generated on the phonological fluency task ($F(1,83) = 1.082$; $p = .301$). However there was a sex difference in the number of repetitions ($F(1,83) = 12.156$; $p < .001$), with men producing more repetitions than women. There was no sex difference for intrusions ($F(1,36) = .885$; $p = .350$).

3.5.1.6 Category Fluency

There was a sex difference favouring women for the number of words generated on the category fluency task ($F(1,83) = 7.639$; $p = .007$). Men also produced more repetitions ($F(1,83) = 25.359$; $p < .001$) and intrusions ($F(1,83) = 6.519$; $p = .013$) than women.

3.5.1.7 Inhibition Task

There was a significant main effect of sex (F (1,82) = 19.779; p<. 001) favouring men for accuracy on the inhibition task. A main effect of trial type (F (1,82) = 59.473; p<. 001) and condition (F (1,82) = 1472.556; p<. 001) was reported. There was also a significant three-way interaction (trial type x condition x sex) (F (1,82) = 37.745; p<. 001). A series of two-way ANOVA's examining each condition (forwards and backwards) separately by gender were then carried out to explain this three-way interaction. In the forward condition there was a main effect of sex for the F23 condition (F (1,82) = 13.110; p<. 001) and no main effect of sex for the F77 condition, showing that men and women do not differ in performance on the F77 trials. In the backward condition, however, there was a main effect of sex for both the B23 (F (1,82) = 13.923; p<. 001) and the B77 trials (F (1,82) = 38.149; p<. 001, see figure 3.3). Post hoc t-tests reveal that men performed better than women during all conditions and trial types (F23, B23 and B77) except for the F77 where no sex differences were found (see table 3.2).

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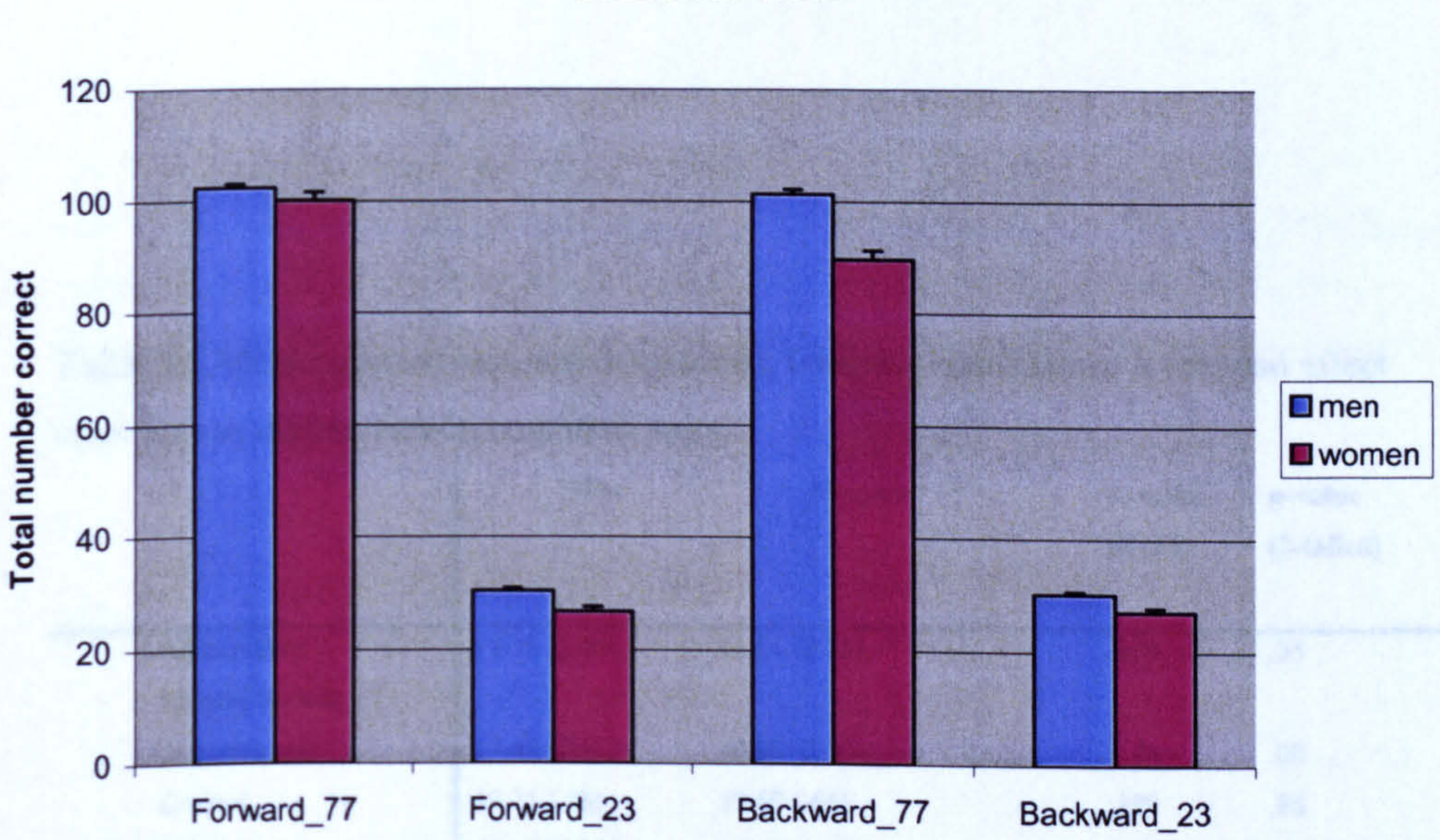
For response latency there also was a main effect of sex (F (1,82) = 10.310; p<. 001) favouring men. There was also a main effect of trial type (F (1,82) = 45.140; p<. 001) but no main effect of condition (p>.0.5). A three-way interaction (F (1,82) = 13.220; p<. 001) was also found. A series of two-way ANOVAs examining response latency for each condition (forwards and backwards) separately for men and women followed by post-hoc mean comparisons were then carried out to find the locus of this three-way interaction. In the forward condition there was a main effect of sex for response latency on the F23 (F (1,82) = 5.958; p= 0.017) and F77 (F (1,82) = 5.181; p=0.025) conditions showing that men and women differed in response latencies on these trials. In the backward condition there was a main effect of sex for response latency on the B77 trials (F (1,82) = 23.011; p<0.001), but not on the B23 trials (p <.05). Post-hoc t-tests revealed that men performed faster than women on all conditions and trial types (F23, F77 and B77) except for the B23 trials where no sex differences was found (see table 3.2).

Figure 3.3 Graph showing the total number corrects (with error bars for standard error of mean) for all the conditions of the inhibition task.



3.5.1.8 Working Memory Task

There were no main effects of sex ($F(1,82) = 2.004$, $p = .161$) or condition ($F(1,82) = .373$, $p = .543$) for accuracy on the N-Back task, but there was a significant condition x sex interaction ($F(1,82) = 4.570$, $p = .036$). Women performed better than men on the 0-back condition, men performed better than women on the 1-back condition and men and women did not differ on the 2-back condition. For response latency, there was no significant main effect of sex ($F(1,82) = 1.233$; $p = .270$), and no significant interaction

(F (1,82) = .929, p = .338). However, as might be expected, there was a significant main effect of condition (F (1,82) = 4.977, p = .028), with both men and women performing faster on the 0- and 1-back conditions than on the 2-back condition.

Table 3.2 Means scores (standard deviations), t-values, significance levels and effect sizes for sex differences on cognitive tasks.

	Men	Women	t- value df (82)	p-value (2-tailed)	Effect sizes
Vocabulary	12.12 (2.58)	11.61 (2.28)	.939	.35	0.20
Mental Rotation [a]					
Experimental	13.65 (2.50)	10.99 (2.60)	4.74	.00	1.04
Control	19.71 (.48)	19.69 (.64)	.199	.84	0.03
MJOLO	15.17 (2.96)	13.19 (2.29)	3.422	.00	0.75
CBJOLO	75.21 (9.47)	64.95 (10.35)	4.74	.00	1.03
Phonological fluency					
Number of words generated	47.64 (12.09)	50.36 (11.82)	1.04	.30	0.23
Number of repetitions	1.86 (3.17)	.14 (.35)	3.48	.00	0.98
Number of intrusions	.14 (.42)	7.14E-02 (.26)	.941	.35	0.20
Category Fluency					
Number of words generated	48.50 (9.72)	54.52 (9.99)	2.800	.00	0.61
Number of repetitions	3.17 (3.19)	.52 (1.19)	5.025	.00	1.21
Number of intrusions	.26 (.66)	.00 (.00)	2.553	.01	0.78
Inhibition [b]					
F23	30.38 (3.38)	26.86 (5.33)	3.62	.00	0.81
F77	102.29 (4.70)	100.07 (9.36)	1.37	.17	0.50
B23	30.19 (3.16)	27.21 (4.09)	3.73	.00	0.82
B77	101.26 (5.87)	89.64 (10.69)	6.17	.00	1.40
Working memory					
Percentage correct on	94.96 (7.12)	97.30 (2.69)	2.21	.03	0.47

the 0 Back condition					
Percentage correct on the 1 Back condition	79.45 (17.92)	69.69 (21.62)	2.25	.02	0.49
Percentage correct on the 2 Back condition	58.35 (21.69)	51.31 (19.42)	1.56	.12	0.34

Table 3..2

[a]Data are means (s.d), df =81, n =41 men, 42 women.

[b]F23= correct responses in which 23% of the numbers are presented in a backward direction, F77= correct responses in which 77% are in the forward direction, B23 = correct responses in which 23% of the numbers are presented in a forward direction, B77= correct responses in which 77% are in the backward direction.

3.5.2 Hormones and Task Performance

Tables 3.3 and 3.4 display the correlations between hormones and task performance for men and women, respectively. Correlations were carried out for accuracy data, because sex differences were found more consistently for accuracy than for response latency. There were 4 significant correlations between hormones and cognitive performance in women and 7 in men.

For women, SHBG correlated positively with the experimental condition of the mental rotation task ($r = .365$, $p = .018$), FSH correlated negatively with performance on the MJOLO task ($r = -.416$; $p = .006$), and both LH and FSH correlated negatively ($r = -.341$; $p = .006$) and ($r = -.314$; $p = .043$) with performance on the F23 condition of the inhibition task.

For men, all correlations involved the inhibition task. FSH correlated negatively with B77 performance ($r = -.340$; $p = .028$), LH correlated negatively with F77 ($r = -.330$; $p = .033$), B33 ($r = -.351$; $p = .023$) and B77 ($r = -.355$; $p = .021$) performance, and P correlated positively with F23 ($r = .423$; $p = .005$), F77 ($r = .473$; $p = .002$) and B30 ($r = .343$; $p = .026$) performance.

Bonferroni corrections for multiple comparisons revealed no significant relationships between hormones and cognitive performance ($P > 0.05$).

Table 3.3

Correlations between gonadal hormones and performance on cognitive tasks for men.

	E	*FSH*	*LH*	*P*	*T*	*SHBG*
Vocabulary	.080	.047	-.071	-.033	-.162	-.087
MR	-.043	-.096	-.049	-.240	-.044	-.179
Experimental						
MR Control	-.261	.044	.027	.153	-.136	-.042
BCJOLO	.010	-.009	-.035	-.139	.060	-.004
MJOLO	.053	.167	.033	-.033	.143	.018
Phonological Fluency	.165	.150	.159	.027	.152	.071
Category Fluency	.156	-.118	.031	.010	-.098	-.129
Inhibition						
F23	.041	-.159	-.283	.423**	-.022	-.057
F77	.200	-.217	-.330*	.473**	.092	.158
B23	.103	-.167	-.351*	.343*	-.147	-.017
B77	.198	-.340*	-.355*	.295	.018	-.034
Working						
Memory						
0-Back	.186	-.247	.048	-.003	.123	-.176
1-Back	-.112	.034	-.209	-.071	.221	.061
2-Back	.015	.009	-.050	.080	.279	.181

MR = Mental rotation

*** < 0.05 ** <0.01**

Table 3.4

Correlations between gonadal hormones and performance on cognitive tasks for women.

	E	*FSH*	*LH*	*P*	*T*	*SHBG*
Vocabulary	.199	-.193	-.303	.046	.027	.032
MR	-.245	-.060	-.142	-.046	-.020	.365*
Experimental						
MR Control	.062	-.010	.035	.008	.116	-.091
BCJOLO	-.107	.064	-.116	.016	-.021	.035
MJOLO	.098	-.416**	.090	.142	-.105	-.032
Phonological Fluency	.012	-.037	-.341*	-.047	.113	-.114
Category Fluency	-.188	.090	-.230	.011	.032	-.066
Inhibition						
F23	-.025	-.314*	-.073	.288	.006	.026
F77	.267	-.062	-.014	.152	.128	.188
B23	.193	.024	-.149	.042	.065	.043
B77	.019	-.272	-.081	.148	-.032	.193
Working Memory						
0-Back	.200	.131	.204	-.042	-.018	.196
1-Back	.113	-.136	-.233	.066	.298	.151
2-Back	.178	-.159	-.295	.055	.135	.149

MR = Mental rotation

*** < 0.05 ** <0.01**

3.5.2.1.Partial Correlations and Free T

Partial correlations, controlling for SHBG, revealed no significant relationships between performance on any of the cognitive measures and T or E, for either men or women (all p's >. 05). Also, no significant relationships were found between levels of free testosterone and performance on any of the cognitive tasks (all p's >. 05) in either men or women.

Table 3.5 Partial correlations between E and T (controlling for SHBG) and cognitive tasks and Pearson's correlations between the concentration of Free T and cognitive tasks.

	Men			Women		
	Partial correlations			Partial correlations		
Cognitive Abilities	E	T	Free T	E	T	Free T
Vocabulary	.069	-.143	-.123	.197	.027	.009
MR Experimental	-.088	.041	.077	-.294	-.010	-.155
MR Control	-.278	-.131	-.122	.069	.113	.172
BCJOLO	.014	.070	0.81	-.114	-.020	-.028
MJOLO	.075	.153	.176	.098	-.106	-.122
Phonological Fluency	.189	.133	.129	.019	.110	.118
Category Fluency	.113	-.042	.008	-.186	.030	.051
F23	.007	.015	-.023	-.027	.007	.003
F77	.228	.017	-.021	.257	.136	.037
B23	.099	-.174	-.225	.187	.066	.038
B77	.169	.056	-.007	.006	-.027	-.082
0-Back	.149	.249	.309*	.188	-.012	-.097
1-Back	-.076	.220	.227	.100	.306	.199
2-Back	.089	.220	.205	.168	.141	.070

* < 0.05 ** <0.01

3.5.2.2 Curvilinear Relationships

There were no significant curvilinear relationships between any of the spatial tasks and T in either men or women (mental rotation: men R = 0.120, p = .491, women R = 0.134, p = .407; BCJOLO: men R = 0.135, p = .448, women R = 0.157, p = .331; MJOLO: men R = 0.149, p = .530, women R = 0.269, p = .116).

3.6 Discussion

Overall, the results of the present study confirmed the hypotheses regarding sex differences in cognitive performance as suggested by previous research (Hyde and Linn, 1988, Halpern, 1992, Voyer et al., 1995). Sex differences favouring men were found for performance accuracy on the spatial tasks (mental rotation, MJOLO and the BCJOLO), whilst women outperformed men on the category fluency task. However, there was no female advantage in letter fluency, which was contrary to expectation. This could have occurred because the letter fluency task usually elicits a relatively small sex difference (Hyde and Linn, 1988; see Table 3.2 for effect sizes for sex differences in the current study). However, men made significantly more repetitions on this test compared to women, which may indicate that they have problems with some aspect of this task. The working memory task, was performed better by women on the 0-Back condition, and by men on the 1-Back condition. The finding for the 0-back condition, which does not involve memory, may be additional evidence that women perform better than men on perceptual motor tasks (Broverman et al. 1968, Halpern, 1992). However, this is the first study, which has looked at sex differences on this working memory task. Also as expected, no sex differences were seen on the vocabulary test, a measure of general intellectual ability that was included for control purposes, and therefore sex differences in cognitive performance cannot be attributed to differences in IQ.

Another novel aspect of the present results is the observation of sex differences on computerized versions of the mental rotation, judgment of line orientation and working memory tasks. Most previous studies of sex differences in spatial performance have used paper and pencil measures of these abilities (Voyer et al., 1995; Hyde and Linn, 1988). The findings of this study are contrary to suggestions that computerized versions of mental rotation tasks show smaller sex differences than paper and pencil versions (Voyer et al., 1995). The sex differences we observed for computerized versions of three-dimensional mental rotation (d=1.04) and BCJOLO (d=1.03) were large and compare favourably with effect sizes for paper-and-pencil versions of the same tasks (Voyer et al., 1995; Hyde and Linn, 1988). The existence of large sex differences on computerized

versions of these tasks extends their usefulness. For example, they could be used in (f)MRI studies of neural activation during task performance, where paper and pencil tasks are not workable.

Furthermore, the present study also found that when a modified version of the BCJOLO was used, which is designed to be more difficult, men and women performed better on this test (MJOLO) as seen in the percentages correct for men and women on each task. Thus, showing that the subjects in the current study did not find the MJOLO test to be more difficult compared to the BCJOLO, even though the effect size for the BCJOLO was larger than the MJOLO test. These observations may have occurred because, firstly, the MJOLO test is a paper-pencil measure, whereas the CBJOLO was computerized. Secondly, there was no time constraint to complete the MJOLO test, whereas there was a time limit of 2.5 seconds to respond to each stimulus on the BCJOLO task.

In addition, the present data provide the first confirmation of the hypothesis that men are better than women at inhibiting their responses to obvious stimuli (counting forwards) in favour of less obvious stimuli (counting backwards). The hypothesis of this study, that such a sex difference might exist, derived from Broverman et al. (1968), who suggested that men are better than women at inhibitory perceptual restructuring, which requires separating certain stimulus attributes from the context in which they are embedded.

Despite observing the expected sex differences on tasks, however, the present study found none of the hypothesized relationships between hormones and cognitive performance. For three of the eight cognitive tasks, (two that showed sex differences, BCJOLO and category fluency, and a control measure that did not, vocabulary) there were no relationships to hormones, either predicted or unpredicted, for men or women. For 5 tasks (mental rotation, phonological fluency, working memory, MJOLO and the inhibition task) there were some associations with P, SHBG or gonadotropins (LH and FSH). However, none of the significant correlations corresponded to what had been hypothesized based on prior reports.

In regard to hypotheses involving T, this study found no relationship between T and any of the spatial tasks. These findings contrast with some reports (Janowsky et al., 1994; Christiansen, 1993; Christiansen and Knussmann, 1987), but are consistent with others (McKeever and Deyo, 1990; Gordon et al, 1986). The procedures of this study were most closely similar to those of Christiansen (1993) and Christiansen and Knussmann, (1987) who also used a single measure of endogenous T, taken in the early morning. One possible explanation for inconsistencies between the results of this study and the results of theirs is the use of different measures. For example, this study used measures of mental rotation and judgement of line orientation, whereas Christiansen and Knussmann (1987) used different measures of spatial ability, including Block Design, Concealed Figures and Embedded Figures. Christiansen (1993), on the other hand, used tactual-spatial functioning, field independence/field dependence tests. However, the tests used in the present study showed substantial sex differences, whereas sex differences on the measures used by Christiansen (1993) and Christiansen and Knussmann (1987) such as Block Design, Concealed Figures and Embedded Figures (see Collaer and Hines, 1995) typically do not, and they did not include female controls preventing assessment of sex differences among participants in their studies. Given that sex steroids are hypothesized to relate specifically to measures that show sex differences, it is puzzling that their measures, but not the measures used in this study, related to sex steroids.

The current study also did not find the hypothesized associations between E and verbal fluency, or between E and any of the spatial tasks. Although findings contrast with some prior reports (Hampson, 1990a, 1990b; Silverman and Phillips, 1993), they are consistent with those of Gordon and Lee (1993), who also did not find a relationship between E, P, LH or FSH and verbal or spatial abilities. A more recent study looking at endogenous levels of E in older men and women also did not find any relationship between E and verbal fluency in women, although a negative relationship of verbal fluency to T was seen in men (Wolf and Kirschbaum, 2002).

Studies of E treatment in postmenopausal women have revealed inconsistent results. One study found that women on E replacement therapy performed better on verbal fluency

and working memory tests compared to men (Miller et al., 2002), whereas in a larger sample of postmenopausal women with coronary heart disease taking E replacement therapy, Grady et al. (2002) found that women on E treatment scored worse on verbal fluency tests compared to women on placebo. Similar effects of E on verbal memory have been reported in postmenopausal women (e.g. Maki et al., 2001; Wolf et al., 1999), but these effects have not always been found (Binder et al., 2001; see also Blanc et al., 2001 for review).

With regard to natural fluctuations in E, women have generally been reported to perform worse on verbal fluency tests during the low E phase of the menstrual cycle. The aim of this study, however, was not to compare verbal abilities of women during different phases of the menstrual cycle, but to examine sex differences in cognitive abilities between men and women, and to relate these to endogenous levels of hormones. It was not the intention of this study to test women during the high E phase of the menstrual cycle because, firstly, it is known that the high E phase relates to performance on verbal fluency tests (Hampson, 1990; Maki et al., 2002). Secondly, the study aimed to investigate whether any relationship between low E and verbal fluency tests existed, thus avoiding generalizing to all phases of the menstrual cycle. Lastly, testing women during the high E phase may affect performance on other tests in the cognitive battery and thus influence the data with regard to between subject differences. In addition, although Epting and Overman (1998) found sex differences on 5 out of 6 sex-sensitive tasks in men and women, they found no support for Hampson and Kimura's (1992) hypothesis of phase-related performance differences on any task, and, similar to the present study, their results were consistent with those of Gordon and Lee (1993) and Gordon et al. (1986). In fact, sex differences in verbal abilities have been reported to appear in the absence of any influence of gonadal hormones (Kimura, 1999).

Another finding of the current study, which may also relate to E, is the poor performance of women on the 1-Back condition of the working memory task. The low levels of E in this sample may be a possible reason for this observation, since E treatment has been

reported to facilitate performance on working memory tasks in postmenopausal women (Duff and Hampson, 2002; Keenan et al., 2001).

The results of this study failed to support the hypothesis for a curvilinear relationship of T to any of the three spatial measures in either men or women. Moffat and Hampson (1996) reported that salivary T showed a curvilinear relationship to spatial cognition in a group of men and women combined. Because men have higher T levels than women, this could have reflected a negative relationship between T and performance in men, and a positive relationship in women. They did not analyse their data separately for men and women, however. Regardless, this study did not find a negative relationship between T and any aspect of spatial ability in men or a positive relationship in women, in addition to seeing no curvilinear relationship in either sex.

In relation to hypotheses regarding gonadotropins and cognitive performance, the present study found that FSH correlated negatively with one of the spatial tasks (MJOLO) in women. This replicates the finding of Gordon and Lee (1986). However, this study did not replicate Gordon and Lee's (1986) report of relationships between FSH and spatial abilities in men, or between FSH and phonological or category fluency in women.

For LH the results showed no relationships to performance on verbal tasks in men or on spatial tasks in men or women. These findings contrast with those reported by Gordon and Lee (1986). In addition, the results showed a negative relationship between LH and phonological fluency in women, whereas a positive relationship was found between LH and a word production test in Gordon and Lee's (1986) study. However the phonological fluency task did not show a sex difference in the current sample, perhaps limiting this study's ability to detect relationships of this particular task to hormones. Overall, the results are largely unsupportive of Gordon and Lee's (1986) initial findings. These conflicting results are puzzling, and it is difficult to disentangle the relationship between cognitive tasks and gonadotropins levels. Few studies have examined relationships between gonadotropins and cognitive performance. To better understand these

relationships, future studies need to take these hormones into account when looking at both normal and clinical samples in relation to cognitive performance.

The positive relationship between SHBG and mental rotation performance in women also is a novel finding. SHBG binds to both T and E, rendering them biologically inert (Quissell, 1993). Thus, this study addressed SHBG because positive relationships between gonadal hormones and cognitive abilities (although these were not found) are more meaningful when SHBG levels are taken into account. In relation to the present study, this finding may suggest that, when E is less able to act (due to higher SHBG levels), performance on the mental rotation task is improved in women. The binding of SHBG to T might be predicted to have the opposite effect (i.e. reduce mental rotation performance), however, when E and T were correlated with cognitive performance while controlling for SHBG, no significant relationships were seen.

In addition, the present study found a significant correlation between the concentration of free T and performance on the 0-back condition of the working memory task. Again this is a novel finding, and one that requires replication; more studies would need to be conducted investigating the relationship of gonadal hormones to performance on working memory tasks in order to see whether this relationship exists in men.

Although the findings showed a number (13) of significant associations between hormones and tasks that showed sex differences, these could have been due to the number (352) of uncorrected comparisons. Overall, the study was unable to find support for most of the specific hypotheses derived from prior reports. No associations between hormones and cognitive performance were apparent, even in the face of a robust study design. The present study used measures that showed large sex differences and rigorous hormonal assessment techniques. The present study also controlled for the time of day when samples were taken and for menstrual cycle phase. Although one cannot rule out the possibility that larger samples might have produced significant results, the magnitude of the correlations observed argues against anything but small relationships between the abilities measured and endogenous levels of gonadal hormones or gonadotropins. Also, it

may be that the scattering in the literature of positive and negative correlations between T and spatial ability represent Type I statistical errors, and no actual relationship exists. In addition, given that women were tested during the low E phase of the menstrual cycle, one may argue that there may be too little variability in hormone levels for effects to be seen. However, the range of values (see Table 3.1) suggests that this is not the case. For men, this does not apply and this study represents a failure to replicate prior finding relating a single measure of endogenous T to spatial ability (Christiansen, 1993; Christiansen and Knussmann, 1987)

The present study examined relationships between endogenous levels of hormones and performance on cognitive tests that show sex differences. The results reinforce prior findings of sex differences on certain cognitive tasks, and suggest that the size of these sex differences are at least as large using computerized versions of tasks as with paper-and-pencil assessments. It appears that studies of hormonal manipulations in men and women and fluctuating hormone levels in women have more often shown a relationship to cognitive abilities compared to studies relating a single measure of endogenous hormone levels to performance.

Chapter 4

Study 2: The Relationship of Sex Hormones and Cortisol to Cognitive Functioning in Schizophrenia

4.1 Abstract

Gonadal as well as stress hormones have recently been implicated in pathophysiology and sex differences in onset, prognosis and treatment of schizophrenia. The present study investigated the effects of serum levels of estrogen, progesterone, testosterone, and cortisol on neuropsychological functioning and psychopathology in a group of 37 patients (17 women, 20 men) with schizophrenia. Neuropsychological measures included tests of attention, verbal abilities, language, memory, executive functioning, motor and speed of information processing. The results showed that estrogen and age was associated with low positive symptom scores, and within gender cortisol predicted poor performance on the information processing domain in men. These findings demonstrate that cortisol, in addition to the commonly reported effects of estrogen, influences neuropsychological functioning in schizophrenia with differential effects on specific domains of cognitive functioning, and they underscore the need for further investigation of the modulating role of hormones on neuropsychological functioning in schizophrenia.

4.2 Introduction

The present study is the first attempt, to my knowledge, to examine the relationship of earlier mentioned gonadal hormones as well as cortisol to cognitive performance and symptomatology in schizophrenia patients of both sexes. Based on the limited extant literature, we made the following predictions: (i) estrogen would be associated with lower positive symptom scores and better cognitive performance in men and women, and (ii) cortisol levels would be related to poor performance on memory and frontal lobe tasks and symptom severity in patients.

4.3 Methods

4.3.1 Participants

A group of 37 patients (20 men and 17 women) aged between 18-61 (Mean = 43.81, SD = 10.57), from both inpatient and outpatient settings, with a diagnosis of DSM-IV schizophrenia, as assessed by the Structured Clinical Interview, patient version (SCID-P; Spitzer et al., 1990), participated. All patients were right handed as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). Psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987). All patients were on conventional antipsychotic treatment for 6 weeks or more before taking part in this study. A qualified physician examined the current physical health of patients. Subjects were not included in the study if they had any known endocrine abnormalities, neurological diseases, or were using illicit drugs. Women were excluded if they were pregnant or lactating, were taking any synthetic steroids including the oral contraceptive pill. See Table 2 for clinical and demographic characteristics of patients with schizophrenia. The protocol of this study was approved by the Institute of Psychiatry and Maudsley Hospital Ethical (Research) Committee. After comprehensive description of the study to the subjects, written informed consent was obtained.

4.3.2 Hormonal Assays

A blood sample (10 ml) was taken prior to cognitive assessments for measures of estradiol, testosterone, progesterone, lutenizing-hormone, follicle-stimulating hormone, prolactin and cortsiol. Samples were stored at – 40 °C. All samples were taken at the same time of day (10.00-12.00 hrs) for all subjects to control for circadian variation in hormone levels. In addition, subjects were asked to refrain from smoking cigarettes for 30 minutes prior to hormone sampling, in order to prevent a state of smoking withdrawal affecting the cognitive testing or a heavy intake affecting the hormonal assays. An Advia centaur supplied by Bayer Diagostics, Newbury, Berkshire was used to measure estradiol, progesterone, testosterone, lutenizing hormone, follicle-stimulating hormone

and cortisol. This technique is a sandwich immunoassay using direct chemiluminesent technology. The serum samples for men and women were batched and run in the same assay to avoid any possible bias produced by inter-assay variation. Menstrual cycle phases were not controlled in this study since antipsychotic medication makes it difficult to infer hormonal status in women with schizophrenia (Canuso et al., 2002).

4.3.3 Cognitive Assessments

All patients were administered a comprehensive neuropsychological battery between 10.00 -12.00 hrs by a trained psychologist (RH). The battery included measures of memory, executive function, attention, spatial-motor ability, motor ability, speed of information processing and language ability (see Table 1), and took an average of 1 ½ to 2 hours to complete. Every patient received the same order of tests, and they were given breaks between testing to reduce the effects of fatigue.

The following is a brief description of the neuropsychological tests used:

4.3.3.1 Intellectual Ability

4.3.3.1.1 Premorbid Intelligence

The intellectual status of an individual before the signs of illness was assessed with the National Adult Reading Test (NART) (Nelson, 1982). In this test subjects are presented with a series of words (e.g. Prelate), and they are asked to read the words out aloud. A total of 50 phonetically irregular words are presented and the number of errors made on this test is recorded.

4.3.3.1.2 Current Intellectual Functioning

Current intellectual functioning was assessed using the vocabulary sub-test of the Wechsler Adult Intellectual Scale-Revised (WAIS-R, Wechsler, 1981). In this test

subjects are aurally presented with a word (e.g. winter) and subjects are asked to say what they think this word means. The subject scores 0 for an incorrect response, and 1 or 2 points depending on the detailed description of their answer. The raw score (which is a maximum of 66) is then converted to an age corrected scaled score using the conversion tables provided in the WAIS-R manual.

4.3.3.2 Executive Functioning

4.3.3.2.1 Wisconsin Card Sorting Test

The WCST (WCST, Heaton 1993) is a commonly used test of executive functioning, measuring cognitive flexibility, maintenance of a cognitive set, and working memory (Heaton et al.,1993). Patients with schizophrenia were administered the computerised version of this test. In this test, subjects match a card presented at the lower half of the computer screen to a set of four target cards on the top half of the screen. The subjects are required to work out a sorting rule for the cards that can be characterised by three dimensions, similar colour, similar form (i.e., shape), and similar number of stimuli on the target cards and individual item cards. Subjects are provided with feedback on an item-by-item basis after they sorted each of the item cards. After they identified one of the correct dimensions, referred to as "categories," ten correct responses are required before the correct category is shifted to the next by the computer. Thus, this test requires the subjects to be flexible in their responses by ignoring the previously successful rule and learning a new one. The first category rule the subject has to learn is colour, which then switches to shape and then to number. This sequence of events is repeated once. In these analyses, the critical dependent variables are the total number of categories completed and the total number of perserverative errors made.

4.3.3.2.2 Trail Making Test, Form B

Form B of the trail-making test (Reitan and Wolfsonk, 1958) is another executive functioning test (e.g. flexible thinking, strategy use and planning), which also requires attention and working memory. In this test, subjects are presented with a sheet of paper, printed with a series of letters (A-L) and numbers (1-13) randomly scattered on the paper. The subjects are instructed to join the numbers in ascending order from 1 to 13, alternating with the letters in alphabetical order. The variable of interest on this task is the time taken to complete the test successfully.

4.3.3.2.3 The Maze Sub-Test of the Wechsler Intelligence Scales for Children

The Maze sub-test of the Wechsler Intelligence Scales for Children (WISC-R, 1974). This is another test that assesses executive functioning and it specifically measures strategy use and forward planning. In this test, subjects are instructed to complete 8 mazes, out of which two are practice trials. The mazes start off as easy and progressively become more difficult. The main variables of interest are (1) the total time (seconds) to complete all the mazes, (2) the total number of mazes completed without any errors, (3) the total number of errors made on the mazes (excluding the two practice trials).

4.3.3.3 Attention

4.3.3.3.1 The Continuous Performance Test, Identical Pairs Version

The continuous performance test, identical pairs version (CPT-IP, Cornblatt et al., 1988) test is administered on the computer and is designed predominantly to assess vigilance and the ability to sustain attention (Cornblatt et al., 1989). In this test, subjects are required to identify the pairs of identical numbers within a continuously presented string of four-digit target stimulus numbers that appear flashing on a computer screen at a rate of one per second and remains on the screen for 50 milliseconds (ms). During the task, subjects are instructed to press down on the left button of the mouse pad of the computer

continuously throughout the test and lifting as quickly as they can and putting it back on the mouse button, when the subjects identifies numbers (string of four) which are identical to the ones in the preceding trial. The test also consists of a number of catch trials, this is when the numbers presented on a single trial are similar but not identical to the numbers presented in the preceding trial. Four hundred and fifty numbers are presented in total, out of which 90 are response targets and 90 are catch trials. Performance of individuals on the CPT-IP task is based on hits (i.e. responses to target trials) and false alarms (i.e. responses to catch trials) which yields two signal detection indices: d'prime – sensitivity of the subjects to discriminate targets from catch trials, and beta (change to symbol) – criterion of the subject to respond to target or catch trials. The variables of interest on this test are the d'prime, as a measure of sensitivity or attention capacity and beta as a measure of response strategy.

4.3.3.3.2 Stroop Test

The Stroop (Stroop, 1935) test assesses attention as well as executive functioning processes (planning and use of strategy). Specifically, this test measures the inhibition of pre-potent responses. This Stroop test is based on the idea that it takes longer to say out aloud the coloured names of coloured patches compared to reading words, and even longer to read printed names of colours when the ink is in a different colour than the name of the colour word. There are three parts to the version of the test that has been used in this study. In the first part, subjects are required to read out aloud as many names of colours printed in black ink in 45 seconds. In the second part, subjects are asked to read out aloud colour of a string of X's (e.g. XXXXX in blue). Finally, in the third part of the test, subjects are asked to read out aloud the colour of words that are typed in incongruent coloured ink (e.g. the word BLUE typed in RED, the subject has to say 'RED').

The variable of interest is the interference score, which is calculated. This score is the difference between a predicted colour word (CW) score and the raw CW score. The predicted CW score is calculated from the following formula: C x W/C + W. Age scaled T interference score is derived from the table in the Stroop manual.

4.3.3.4 Learning and Memory

4.3.3.4.1 Bushke Selective Reminding Test

The BSRT (BSRT, Bushke, 1973) is a multi-trial list-learning test, which assesses verbal learning in the form of recall consistency. In this test, subjects are aurally presented with a list of 16 words and the subject is then asked to recall as many of those words as they can remember. In the next trial, only the words that were not recalled in the previous trial are presented to the subject. On each trial the subject has to recall as many words as possible from the list, including the ones recalled on the previous trial. The test stops after the seventh trial or when the subject has recalled all the words. Due to the fact that there are minimal age effects on recall consistency in normal people, the raw recall consistency score will be used as the variable of interest on this test. Also Long term retrieval and total long term storage (the number of words recalled on two or more consecutive trials) short term retrieval (words that are recalled on individual trials), total consistent long term retrieval (words repeatedly recalled without need for reminding), total random long term retrieval (words in long term storage that do not reappear consistently but require further reminding).

4.3.3.4.2 The Hopkins Verbal Learning Test

The HVLT (HVLT –R, Brandt and Benedict, 1999) test assesses free recall and recognition of verbal material. In this test, to measure the free recall component, the subject is presented aurally with 12 words that are derived from three different semantic categories (e.g. animals, drinks, items of clothing) and is then asked to recall as many of those words as they can remember. This is repeated three times and the total number of words recalled on each trial is recorded. The learning trials are followed by a 24-word recognition list containing 12 target words, plus six semantically related and 6 unrelated words that are aurally presented to the subject. The subject is instructed to answer 'yes', if they remember a word from the previous trial and 'no' if they did not recognise the

word. The variables of interest on this test are: (1) free recall: the total number of words recalled over the three trials and (2) recognition: discrimination index for the old and new words.

4.3.3.4.3 Logical Memory, Story Recall (WMS-R)

The number of words and ideas in story recall tests takes them out of the category of tests that measure simple immediate memory span. The Logical Memory test assesses both short (immediate) and long-term memory for short stories, based for example on the weather. In this test the subject is read out aloud two stories and after each story the subject is asked to recall as many details of each of the stories as possible once immediately after the story has been read out (immediate) and then again after 20 minutes (delayed recall). A point is given for each correct detail. Summing the total number of details recalled for both stories during both immediate and long-term retention derives the two variables of interest. The raw scores are then converted to age scaled scores, which are obtained from the WMS-R manual.

4.3.3.5 Verbal Working Memory

4.3.3.5.1 Letter Number Span Test

The letter number test (Gold et al., 1997) assesses the subject's ability to retain and manipulate common verbal and numerical stimuli in working memory. In this test the subject is aurally presented with a sequence of numbers and letters (e.g. A2R). The subject is required to listen to this sequence and to say the sequence out aloud in a specified order, presenting the numbers first in ascending order followed by the letters in alphabetical order (e.g. 2AR). The test begins with easy trials, with two to three stimuli (e.g. one letter, one number, D6), which progressively become more difficult, comprising up to seven stimuli (e.g. three numbers and four letters, C7G4Q1S). The variable of interest for this test is the total number of letter and number sequences completed without any errors.

4.3.3.6 Visuo-Spatial Working Memory

4.3.3.6.1 The Benton Visual Retention Test

The BVRT (Benton, 1972) assesses the ability to maintain and represent visual stimuli from working memory. In this test, the subject is presented with 10 different pictures comprised of abstract shapes in black ink. All but two of each ten card series have more than one figure in the horizontal plane; most have three figures, two large and one small, with the small figure always to one side or the other. Each picture is presented to the subject for 10 seconds and then removed from their sight. The subject is then asked to reproduce that picture from memory on a separate piece of paper. The variables of interest are the total number of pictures reproduced and the total number of errors.

4.3.3.7 Verbal Abilities

Two separate verbal fluency tests (Lezak, 1997) were administered.

4.3.3.7.1 Category Fluency

In this test, subjects are asked to produce the names of as many different animals as possible within a 1-min period, followed by as many fruits as possible and then as many vegetables. The variable of interest is the total number of words generated from all three categories.

4.3.3.7.2 Phonological Fluency

In this test, subjects are asked to produce as many words that start with three different letters, F, A and S for 1 min each, excluding proper names. The variable of interest is the total number of words generated from each letter.

4.3.3.8 Speed of Information Processing

4.3.3.8.1 The Speed and Capacity of Language Processing

The Speed and Capacity of Language Processing (SCOLP, Baddeley et al., 1992) test was developed to assess the efficiency of information processing. In particular, the test allows the assessment of slowing in cognitive processing associated with schizophrenia by measuring the speed of comprehension. The SCOLP test comprises two sub-tests, The Speed of Comprehension Test (SOCT) and The Spot the Word Test (STW). The SOCT is a measure of the rate of the information processing. In this test the subject is required to make judgements on a series of statements (there are a total of 100) as quick as they can in two minutes. This test is followed by the SWT, which is used as a control measure of verbal intelligence and is used as a framework for interpreting the results on the SCOLP test. During the SWT, the subjects are presented with a pair of words one which is a real word, and one of which is a nonsense word. The subject is asked to judge which of the pair of words is a real word and place a tick next to it. There is no time limit on this task. The variables of interest is the discrepancy between the rate of information processing and verbal intelligence, which is derived by subtracting the age scaled score on the SOCT sub-test from the age scaled score on the STW sub-test.

4.3.3.9 Spatial-Motor Ability

4.3.3.9.1 The Groove Peg Board

In the groove peg board test (Kløve, 1963) the subject is presented with a board with keyholes placed in different orientations on the board and a number of metal pegs. The subject is required to insert the metal pegs in the correct orientation of the keyhole on the board, as quickly as they can first with their dominant and then with the non-dominant hand. The two variables of interest are the time taken in seconds to complete the task with the dominant and non-dominant hand.

4.3.3.9.2 Finger Tapping Test

The finger tapping test (Halstead, 1947) is a measure of motor speed and ability. In this test, the subject is required to rest their hand on a wooden board, place their index finger on a metal lever and tap it as quickly as possible in 10 seconds. This is repeated five times for the dominant and then again for the non-dominant hand. The variables of interest are the average number of taps made over the five trials for the dominant and non-dominant hand.

4.3.3.9.3 The Trail Making Test, Form A

Form A of the trail-making test (Reitan and Wolfsonk, 1958) assesses both motor control and speed of visual search, which together provide a sensitive measure of visuo-motor tracking. In this test, the subject is presented with randomly scattered numbers (1 to 25) on an A4 sheet of paper. The subject is required to join the numbers in ascending order as quickly as possible. The variable of interest on this test is the time taken (in seconds) to complete the test.

Table 4.1 Neuropsychological Battery and Alpha Values for the Different Cognitive Domains.

Neuropsychological Variables	Alpha level
Verbal abilities (VERB)	**.8156**
Phonological Fluency	
Category Fluency	
Verbal Memory (VERMEM)	**.8010**
Learning Test (HVLT, Brandt, 1991) Recognition Logical	
Memory (LM, Immediate recall	
LM delayed recall	
HopkinVerbal	
HVLT Discrimination Index	
Bushke Selective Reminding Test (BSRT; Buschke, 1973)	
BSRT Total recall	
BSRT Long term retrieval	
BSRT short term retrieval	
BSRT total long term storage	
BSRT total consistent long term retrieval	
BSRT total random long term retrieval	
Motor (MOT)	**.9411**
Finger Tapper Dominant, (Halstead, 1947)	
Finger Tapper Non-dominant	
Spatial-motor (SPAMO)	**.9775**
Groove Peg Board Dominant	
Groove Peg Board Non- dominant	
Spatial Memory (SPAMEM)	
Benton Visual Retention Test (BVRT) Number correct	
BVRT Number of errors	
Executive Functioning (EXEC; (Heaton, 1983):	**.6788**
Wisconsin Card Sorting Test (WCST) Categories	
Completed	
WCST Perservative Responses	
Trails B (Reitan and Wolfson, 1958)	
WISC-R No. of Errors	
Attention (ATTN)	**-.8087**
Continuous Performance Test (CPT; Cornblatt et al.., 1988)	
D'Prime	
Stroop Interference. Stroop, (1935).	
Trails A (Reitan and Wolfson, 1958)	
Verbal Working Memory (VWM)	
Letter Number (LN)	
Speed of Information Processing (SIP)	
Speed of Comprehension Test (SCOLP)	

4.4 Statistical Analysis

Based on the method of analysing a large battery of neuropsychological tests adopted by previous studies (Bilder et al., 1985; Saykin et al., 1991; Hoff et al., 1992, 2001), internally consistent summary scales were constructed with coefficient alphas ranging from 0.6788 to - 0.8087. The scales were created by converting raw scores into z scores, derived from the means and standard deviations of a normal control group (n = 30) who completed the same neuropsychological battery (not reported in this paper). *A priori* cognitive scales also were constructed based on what each individual test measured. Nine scales (see table 1) were constructed to represent domains of cognitive performance: verbal abilities, verbal memory, motor abilities, spatial-motor, spatial memory, executive functioning and attention. Individual z scores were used to assess speed of information processing using the Speed and Capacity of language Processing Test and verbal working memory (letter number). The use of summary scales enhances the reliability of measurement and reduce type I error by reducing the number of statistical tests needed. The National Adult Reading Test (NART) was administered to measure premorbid IQ and the symbol search and vocabulary subtests of the Weschler Adult Intelligence Scale-Revised (WAIS-R) were used to assess current IQ. All patients were administered the cognitive battery after a blood sample was taken.

Firstly, a series of one-way analysis of variance (ANOVA) were conducted to examine any differences between men and women in each of the nine cognitive domains. Two sets of multiple regression analyses were then conducted to examine the contributions of hormones (estrogen, progesterone, testosterone, cortisol) and symptoms to cognitive performance. The first series of regression models (enter method; probability to enter set at $P < 0.05$) with gonadal hormones and the stress hormone cortisol as predictors of cognitive variables and symptom scores examined the data for the entire sample, and the second series for each sex separately (as there were large differences in levels of circulating sex steroids between the sexes). The above analyses were repeated with age

included as a predictor of cognitive performance and symptom scores. In addition, the analyses were repeated with AOO as a predictor.

4.5 Results

4.5.1 Sample Characteristics

Table 5.2 displays the means and standard deviations for age, education and hormone levels in men and women. There was no significant difference in the conventional medication doses (chlorpromazine equivalents) between men and women. Most (> 70%) of the female patients reported irregular menstrual cycles. For this reason it was difficult to verify menstrual cycle phase for female patients in this study. However, on the basis of estrogen and progesterone levels it was estimated that 7 women were in their follicular phase, 4 in the luteal phase and 6 were postmenopausal. Normal ranges of estrogen for women in the follicular phase is 74-365 pg/ml, luteal 365-1100 pg/ml, postmenopausal <174 pg/ml, progesterone in the follicular phase 2-8 ng/ml, luteal, 30-100 ng/ml. Follicle stimulating hormone: follicular, 4.1-9.5 mIU/ml, luteal, 2.6-9.1 mIU/ml, postmenopausal, 43.7-106 mIU/ml. LH: follicular, 1.6-13 mIU/ml, luteal, 1.1-12.1 mIU/ml, postmenopausal, 13.2-45.7 mIU/ml. testosterone: 0-3 pg/ml, cortsiol: 157-732 nmol/l, prolactin > 500mil/l. For men, normal ranges of estrogen is <184 pg/ml, progesterone, 1.5-5.3 ng/ml, lutenizing hormone, 0.8-6.1 mIU/ml, follicle stimulating hormone, 1.8-8.6 mIU/ml, testosterone: 9-30 pg/ml, cortisol: 255-642 nmol/l, prolactin > 500 ng/ml. (The reference ranges for all hormones are provided by the Laboratory at Guy's Hospital). Within the sample, 9 patients (5 men and 4 women) showed hyperprolactinemia.

Table 4.2 Demographics, Psychopathology and Hormone Levels for Men and Women.

	Men (n=20) Mean (s.d)	Women (n=17) Mean (s.d)	t-value df =(35)	p-value
Education (years)	12.10 (3.77)	11.29 (1.86)	0.80	0.428
Age	40.45 (10.60)	47.76 (9.34)	-2.20	0.034
Age at Onset (years)	24.75 (7.92)	25.59 (10.40)	-0.27	0.783
Premorbid IQ	98.30 (20.88)	103.82 (12.64)	-0.95	0.348
Present IQ	79.25 (17.7)	79.29 (11.17)	0.009	0.993
Medication (chlorpromazine equivalent)	266.95 (285.95)	161.76 (116.34)	1.41	0.165
Score on Positive Symptom scale	22.15 (6.77)	13.17 (5.80)	4.28	0.000
Score on Negative Symptom Scale	22.00 (6.42)	16.47(5.40)	2.80	0.008
Score on General Psychopathology scale	44.50 (10.62)	33.88 (9.86)	3.12	0.004
Total PANNS Score	88.65 (20.06)	63.52 (18.99)	3.88	0.000
Estrogen (pg/ml)	72.35 (50.02)	209.29 (163.53)	-3.56	0.001
Testosterone (pg/ml)	16.65 (7.14)	2.18 (1.92)	8.08	0.000
Progesterone (ng/ml)	2.56 (1.15)	4.50 (10.40)	-0.83	0.412
Cortisol (nmol/l)	400.55 (127.63)	357.11 (136.05)	1.00	0.324
Sex Hormone Binding Globulin (nmol/l)	37.67 (21.00)	43.45 (37.98)	-0.58	0.563
Follicle stimulating Hormone (mlU/ml)	4.49 (2.21)	18.42 (24.61)	-2.52	0.016
Lutenizing Hormone (mlU/ml)	4.97 (2.67)	13.07 (12.93)	-2.73	0.010

Prolactin (ng/ml)	**376.50 (270.34)**	**470.58 (671.09)**	**-0.57**	**0.569**

4.5.2 Sex Differences in Cognitive Domains

There were no significant sex differences in any of the cognitive domains (all p's < 0.05)

4.5.3 Hormones, Symptoms and Cognitive Performance

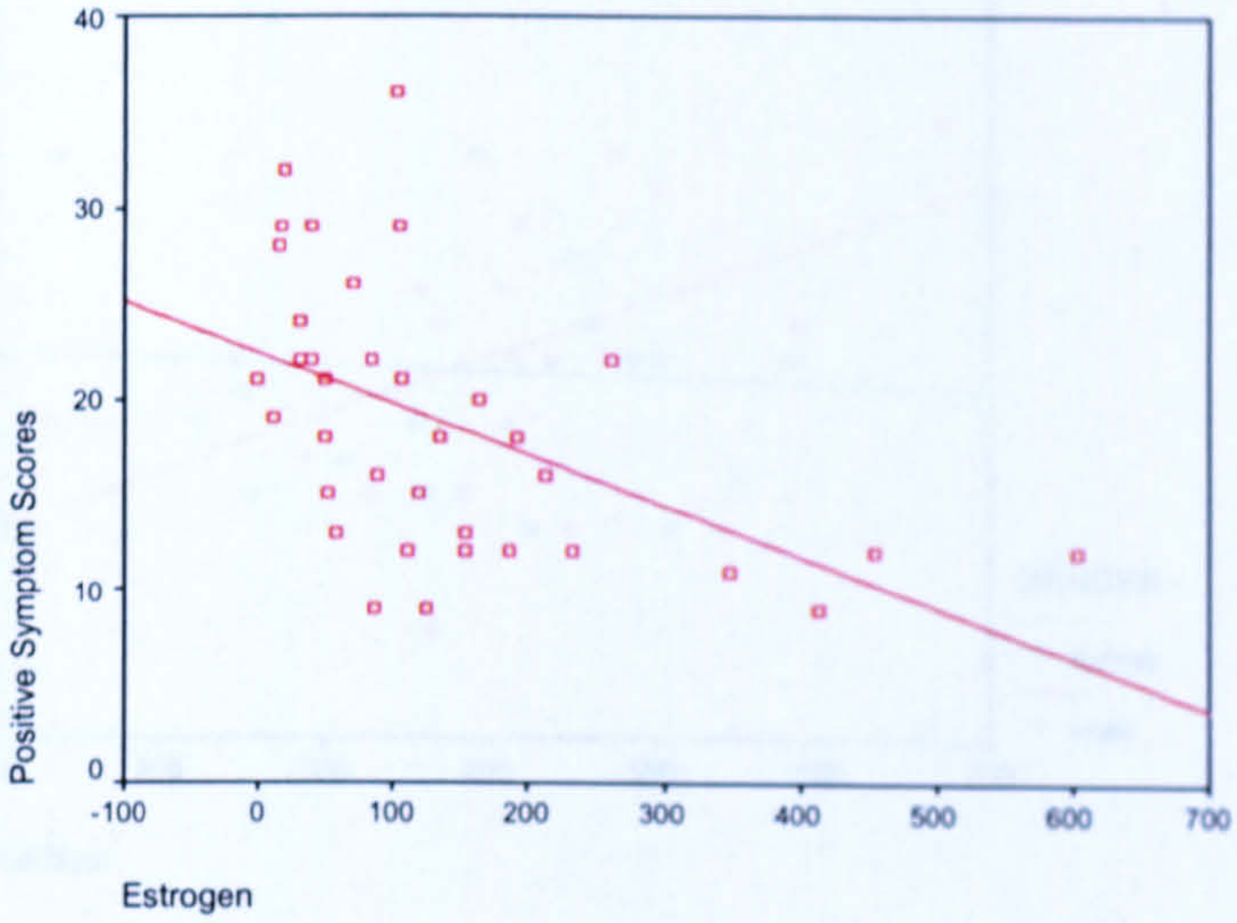
Higher levels of estrogen predicted lower scores on the positive symptom scale (R^2 = 0.332, Adjusted $R^2 = 0.249, p = 0.009$) (Figure 4.1a). No other significant relationships were found between hormone levels and symptom ratings.

Higher progesterone predicted poorer performance on the executive functioning domain ($R^2 = 0.198$, Adjusted $R^2 = 0.098, p = 0.004$). However, this relationship was no longer significant when re-examined with the exclusion of one outlier subject (female) who showed extreme levels of progesterone (Figure 4.1b; this outlier is not included in any analyses reported further).

No relationship was found between any other gonadal hormones or cortisol and any cognitive measures.

Figure 4.1 Scatter plots showing the relationship of (a) estrogen (pg/ml) with positive symptom scores and of, (b) progesterone (ng/ml) with performance on the executive functioning domain.

a



b

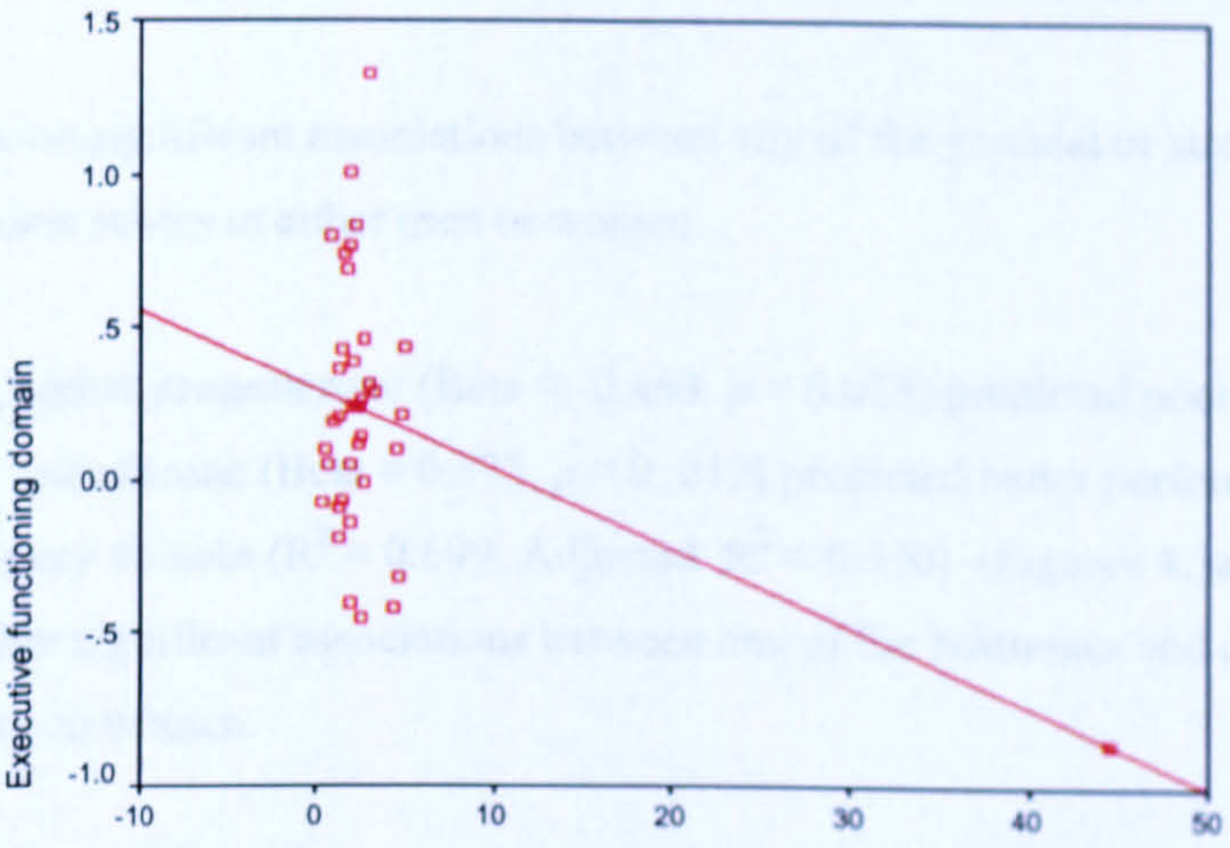
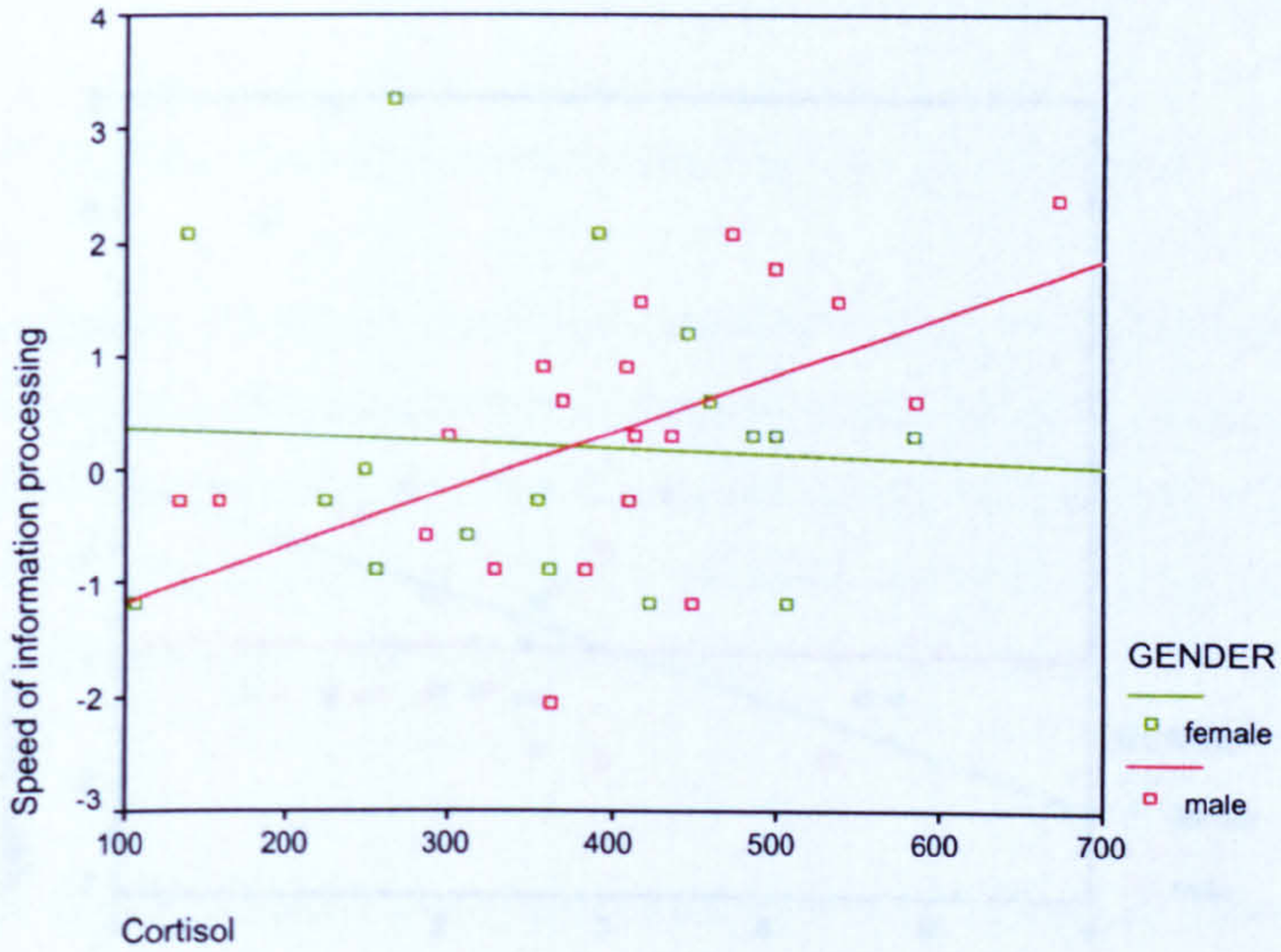


Figure 4.2. Scatterplot showing the relationship between cortisol (nmol/l) and speed of information processing in men and women.



4.5.4 Hormones, Symptoms and Cognitive Performance: Within Gender

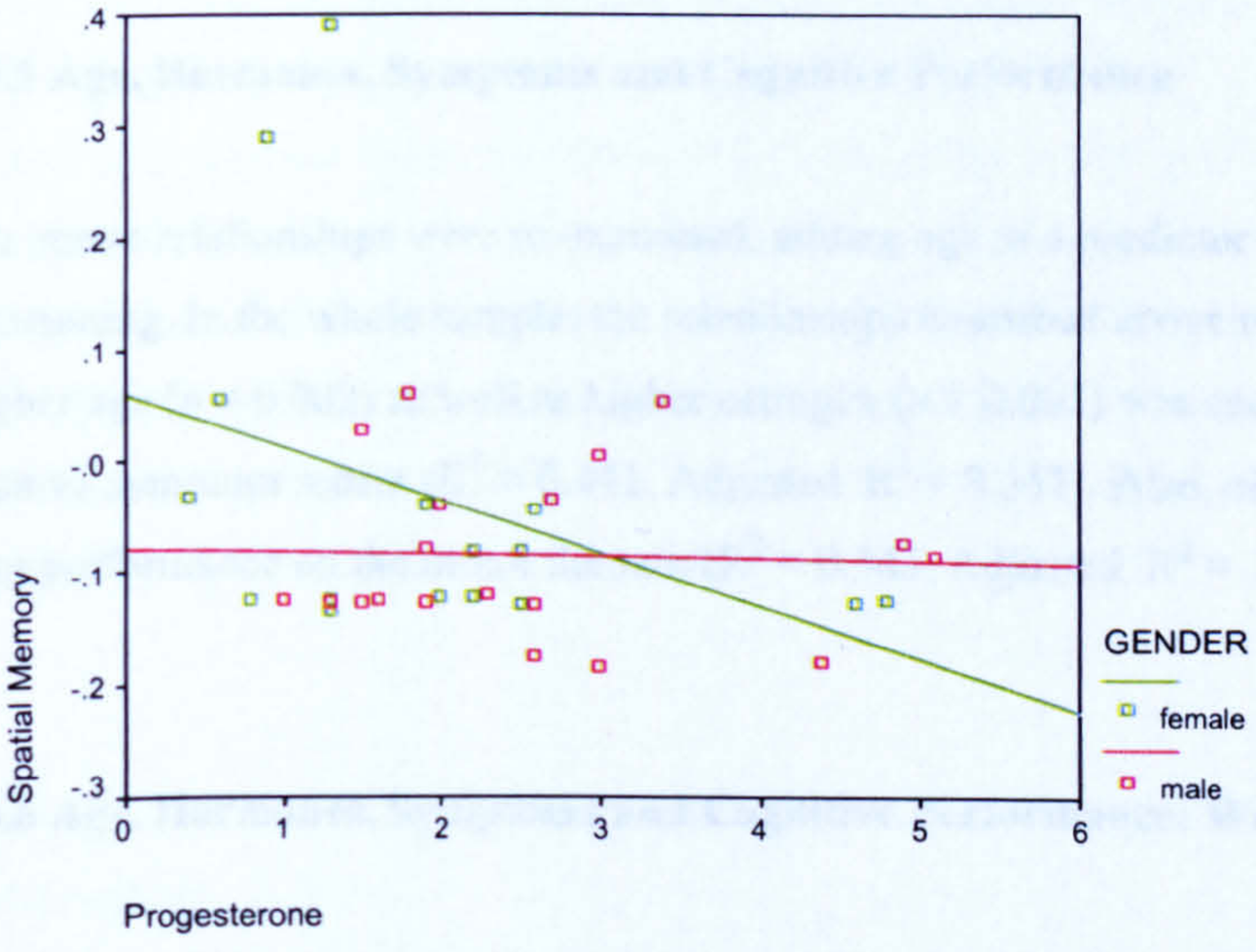
There were no significant associations between any of the gonadal or stress hormones and symptoms scores in either men or women.

In women, higher progesterone (Beta = -0.463, $p = 0.023$) predicted poorer performance and higher testosterone (Beta = 0.573, $p = 0$ .012) predicted better performance on the spatial memory domain ($R^2 = 0.699$, Adjusted $R^2 = 0.590$) (Figures 4.3a and b). There were no other significant associations between any of the hormones and cognitive performance in women.

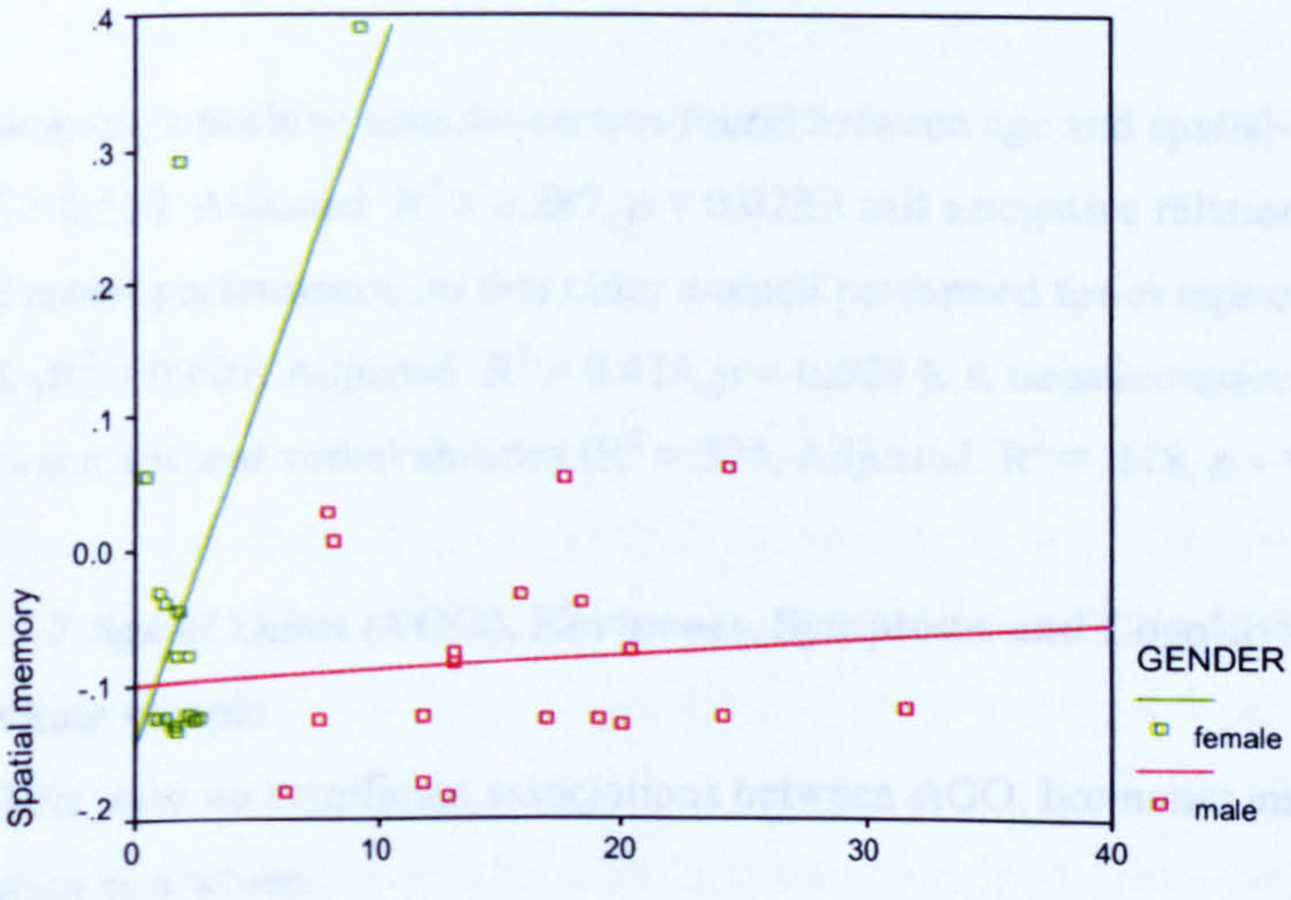
In men, higher levels of cortisol predicted poorer performance on the speed of information processing domain ($R^2 = 0.357$, Adjusted $R^2 = 0.186$, $p = 0.027$) (Figure 4.2). There were no other significant associations between any of the hormones and cognitive performance when examined separately in men.

Figures 4.3. Scatterplots showing the relationship of (a) progesterone (ng/ml) with the spatial memory domain and of (b) testosterone (pg/ml) with the spatial memory domain

a



b



4.5.5 Age, Hormones, Symptoms and Cognitive Performance

The above relationships were re-examined, adding age as a predictor of cognitive functioning. In the whole sample, the relationships described above remained significant. Higher age ($p = 0.002$) as well as higher estrogen ($p = 0.005$) was associated with low positive symptom scores ($R^2 = 0.441$, Adjusted $R^2 = 0.351$). Also, older age predicted poor performance on the motor domain ($R^2 = 0.343$, Adjusted $R^2 = .237$, $p = 0.002$).

4.5.6 Age, Hormones, Symptoms and Cognitive Performance: Within Gender

Analyses including age as a predictor also produced the same results with each sex as described above for findings without the inclusion of age.

In women, a positive association was found between age and spatial-motor performance ($R^2 = 0.510$, Adjusted $R^2 = 0.287$, $p = 0.022$) and a negative relationship between age and motor performance, so that older women performed fewer taps on the finger tapper task ($R^2 = 0.601$, Adjusted $R^2 = 0.419$, $p = 0.008$). A negative association was found between age and verbal abilities ($R^2 = .394$, Adjusted $R^2 = .118$, $p = 0.044$).

4.5.7 Age of Onset (AOO), Hormones, Symptoms and Cognitive Performance: Whole sample

There were no significant associations between AOO, hormones and symptoms in the group as a whole.

In the whole sample a negative assocation was found between AOO and motor performance ($R^2 = 0.241$, Adjusted $R^2 = 0.118$, $p = 0.025$). No other significant associations were found between AOO, hormones and cognitive performance.

4.5.8 Age of Onset (AOO), Hormones, Symptoms and Cognitive Performance: Within gender.

There were no significant relationships between AOO, hormones and symptoms in either men or women.

AOO was positively related to spatial memory ($R^2 = 0.494$, Adjusted $R^2 = 0.263$, $p = 0.017$) and visuomotor performance ($R^2 = 0.483$, Adjusted $R^2 = 0.247$, $p = 0.030$) in women. A negative association was found between AOO and motor performance in men ($R^2 = 0.388$, Adjusted $R^2 = 0.170$, $p = 0.031$).

4.6 Discussion

The main findings of this study were, in the whole sample: (i) estrogen and age related to lower scores on the positive symptom scale and, within sex (ii) higher cortisol predicted poor information processing in men.

The positive relationship of estrogen to positive symptom scores confirms the *a priori* hypothesis of this study. It extends prior findings of an association between estrogen and psychopathology in women in the acute phase of schizophrenia who reported having regular menstrual cycles and were younger than the sample in the present study (Kulkarni et al., 1996; Kulkarni et al., 2001). In addition, the study found this association, for the first time, in both men and women with schizophrenia.

Consistent with previous findings (Thompson et al., 2000), the women in this sample who showed the highest levels of estrogen (usually during the early luteal phase of the menstrual cycle) demonstrated lower symptom scores. Similarly, previous reports have

found that there are more hospital admissions during the low estrogen phase of the cycle compared with the high estrogen phase when symptoms appeared to improve (Riecher-Rossler and Hafner, 2000). These finding corroborate the results of Kulkarni and colleagues, that adding estrogen as an adjunct to antipsychotic medication can improve symptomatology in men and women (Kulkarni et al., 1996, 1999, 2001). Furthermore, premenopausal women have been reported to present a better course of the illness compared to men and have had fewer hospitalisations, shorter hospital stays and require lower doses of antipsychotic medication (Riecher-Rossler and Hafner, 2000; Seeman, 1990). However, it is important to note that the female patients in this sample displayed abnormal endocrine profiles; thus the exact phase of the menstrual cylce is not entirely clear.

The way in which estrogen affects symptomatology is unknown. However, among the mechanisms proposed, most evidence favours the antidopaminergic properties of estrogen (Hafner et al., 1991; Hafner et al., 1993). Evidence from animal studies suggests that estrogen reduces dopamine concentration in the striatum and modulates sensitivity as well as the number of dopamine receptors (Koller et al., 1980; Foreman and Porter, 1980; Dupond et al., 1981; Bedard et al., 1984; McEwen and Woolley, 1994; Di Paolo, 1994). Also, several studies have demonstrated that both estrogen and testosterone, which can be converted to estrogen by the enzyme aromatase, affect the density of 5-HT_{2A} receptor sites and the serotonin transporter in regions of the brain which are associated with the control of mood, mental state and cognition (Summer and Fink, 1997, 1998; Fink et al., 1999).

The association between estrogen and positive symptom scores may be due to other confounding factors, particularly the influence of antipsychotic treatment, the dosage of which depends in part on the psychopathology. While antipsychotic treatment may increase prolactin levels (Kleinberg et al., 1999) and therefore reduce estrogen levels, this study found no statistically significant relationship between prolactin and estrogen levels (data not shown).

In addition to the present hypotheses, the results of this study showed an association between age and positive symptom scores. This finding is of interest and may be related to the long-term treatment of conventional antipsychotics (Youssef, 1991). Furthermore, previous studies have reported a later age of onset in women, which has been associated with reduced severity of symptoms in premenopausal women (Hafner, 2003).

The finding that higher levels of cortisol relate to poorer performance on speed of information processing in men confirmed the hypotheses of this study. Higher levels of cortisol in humans have been found to alter the processes associated with functions dependent on the prefrontal cortex, such as attention regulation and planning, as well as facilitating complex cognitive operations (Lupien et al., 1999; Young et al., 1999). Furthermore, high levels of glucocorticoids have been found to impair hippocampal morphology and thus lead to cognitive impairment (Joels and DeKloet, 1992). However, the fact that the present study did not find any associations between cortisol and memory performance in the sample of patients may be due to the different tests of memory used compared with previous studies (Newcomber et al., 1998; Walder et al., 2000).

With regard to the relationships between hormones and psychopathology, this study did not find any relationship between cortisol and psychopathology. This may be due to reduced range of cortisol or symptom scores.

In the current sample of patients, age was associated with poor performance on the motor functioning domain. The extrapyramidal side effect caused by conventional treatment has been found to relate to poor motor functioning in patients with schizophrenia (Heinz et al., 1998; Fitzgerald et al., 2000). In women, age was associated with better performance on the spatial-motor domain. It is possible that in this study's sample of women, lower estrogen related to older age resulted in better spatial-motor performance. This is consistent with menstrual cycle studies that have reported better spatial performance during phases of the cycle characterised by low estrogen compared with high estrogen (Hampson, 1990a, 1995). Another reason for this finding is that women tend to present symptoms of schizophrenia after having achieved a higher level of social and cognitive

development (Hafner, 2003), which, as demonstrated in the present study, preserves some aspects of cognitive functioning. In addition, Mozley et al. (2001) found relationships between dopamine availability in the caudate and putamen and executive as well as motor functioning in women but not men, thus lending support to the fact that that this relationship may be specific to women with schizophrenia.

The findings of the current study also found positive relationships between AOO and spatial memory and visuomotor performance in women. Also, a negative relationship was found between AOO and motor performance in men, so that older AOO was related to making fewer taps on the finger tapping test. These findings suggest that factors other than sex hormones i.e.AOO can also be a good predictor of performance on cognitve tasks. These findings also outline the fact that other variables such as a detailed endocrine profile taken by a qualified clinician, and duration of illness should be taken into account when conducting such a study.

The present study also found that age was associated with poor performance on verbal abilities in women. This finding is consistent with studies that have found that postmenopausal women perform worse than women taking estrogen therapy on verbal tasks (Miller et al., 2002). In addition, previous menstrual cycle studies have reported that women perform better on verbal tasks during the luteal phase (high estrogen) compared to the follicular phase (low estrogen) of the menstrual cycle (Rosenberg and Park, 2002; Hampson, 1990b).

A novel finding of this study was the positive association of testosterone and a negative association of progesterone to the spatial memory domain in women. This finding is of interest because studies that have administered testosterone to healthy young women have shown improvements in aspects of object location memory (Postma et al., 2000). However, to the writer's knowledge, the relationship of testosterone to spatial memory has not previously been studied in women with schizophrenia. Similarly, the finding of progesterone levels contributing to poor performance and testosterone to better performance on tasks measuring spatial memory suggests that it may be important to

include these hormones in future studies. However, like estrogen, progesterone has been shown to have psychotropic properties in both mammalian species, (Kavaliers and Wiebe, 1987; Bitran et al., 1995; Lancel et al., 1996) and in humans (Bäckström et al., 1984, Friess et al., 1997) after intravenous or oral progesterone. This hormone has been found to act as a functional antagonist at the 5-HT_3 receptor (Wetzel et al., 1998). Furthermore, it has been suggested that variations in the secretion patterns of progesterone may contribute to the development of psychiatric disturbances and dysphoric mood (Brockington and Meakin, 1994; Harris et al., 1994), which may explain the poor performance on spatial memory tasks that was shown in the present study. Certain metabolites of progesterone are reported to be potent and selective positive allosteric modulators of the γ-aminobutyric acid type A ($GABA_A$) receptor. Also, administration of progesterone can demonstrate behavioural effects that include, anxiolysis, sedation and analgesia (Lambert et al., 2003). De Wit et al. (2001) showed that a single dose of progesterone produced mild sedative-like effects in normally cycling women. Similarly, Söderpalm et al. (2004) showed that administration of progesterone in both men and women during the ealy follicular phase of the menstrual cylcle was related to feelings of fatigue and impaired smooth eye pursuit. The finding from these studies may explain the poor performance on spatial memory tasks that were shown in the present study. Importantly, the observation of the present study was found in a naturalistic hormone environment, whereas the finding of a positive relationship between progesterone and scores on the spatial memory domain in Hoff et al.'s (2001) study was observed in women with artificially raised levels of gonadal hormones, as well as consisting of a sample of a severely ill group of early onset patients who would not be representative of women with schizophrenia as a whole.

The results of this study suggest that gonadal hormones, estrogen, progesterone and the stress hormone cortisol as well as AOO relate to cognitive functioning and symptomatology in schizophrenia. There are, however, limitations to this study. Additional research is needed to verify these relationships and examine the mechanisms underlying them. For instance, the present study took blood samples for hormone measures at a single time point. Studies examining relationships of changing hormone

levels, or hormone manipulations to cognitive performance could help elucidate the mechanisms underlying the relationships observed. In addition, because of the small sample of this study and the large number of regressions carried out, it is important that our results be replicated. Nevertheless, the results add to a growing body of work, which suggests that gonadal and other hormones are involved with the cognitive alterations associated with schizophrenia.

Chapter 5

Study 3: Neural Activation to a Mental Rotation and an Overt Verbal Fluency Task in Healthy Men and Women

5.1 Summary

The neural correlates of sex differences in visuospatial and verbal fluency tasks remains unclear. The present study examined behavioural performance and blood-oxygenation-level-dependent regional brain activity, using functional magnetic resonance imaging, during a three-dimensional mental rotation task and a compressed sequence overt verbal fluency task in a group of healthy men (n =9) and women (n =10; tested during the low estrogen phase of the menstrual cycle). Consistent with previous literature, men outperformed women on the mental rotation task and women were superior to men on the verbal fluency task. For the mental rotation task, men and women activated areas in right superior parietal lobe, left medial occipital gyrus and right superior occipital gyrus during the rotation compared with the control condition. Men activated additional areas in left medial temporal gyrus, left precuneus and right angular gyrus, and women activated right postcentral gyrus. For the verbal fluency task men activated areas in bilateral superior frontal gyrus, right cingulate gyrus, left precentral gyrus, left medial frontal gyrus, left inferior frontal gyrus, thalamus, left parahippocampal gyrus and bilateral lingual gyrus, and women activated areas in bilateral inferior frontal gyrus and left caudate during the

letter compared to rest condition. Despite some areas found to be significantly active in any one group, no areas significantly differentiated the two sexes. Both sexes activated similar areas for the mental rotation task and for the verbal fluency task, but achieved a different level of performance. Equal performance in men and women may lead to detectable sex differences in brain activation.

5.2 Introduction

To date, no fMRI study has looked at the role of gender in cerebral activation during performance on a verbal (phonological) fluency task using this method of image acquisition.

The present study applied fMRI to investigate blood-oxygenation-level-dependent (BOLD) regional brain activity during a 3-D mental rotation and an overt verbal fluency task (using a compressed sequence design) in men and women during the low estrogen phase (menses) of the menstrual cycle. The aims of this study were: (i) to examine sex differences in behavioural performance on the mental rotation and verbal fluency tasks (ii) elucidate the neural correlates of performance on the mental rotation and verbal fluency tasks in men and women (iii) to examine for any sex differences in brain activation during performance on these tasks, while controlling the role of estrogen. Based on available data, it was hypothesized that: (1) men would perform better than women on the mental rotation task. (2) women would perform better than men on the verbal fluency task. At the neural level, for the mental rotation task, the expectations for the present study were (3) activation in the parietal areas in both and men and women with a more bilateral activation in men and, (4) for the verbal fluency task activation was expected in left prefrontal areas in both sexes, with more bilateral activation in women.

5.3 METHODS

5.3.1 Participants

Nineteen right-handed, men (n =9) and women (n =10) aged between 20 and 30 years (men M = 25.78 SD = 3.15, women, M = 24.90 SD = 2.28) served as subjects. Based on self-reports, all women reported having regular menstrual cycles, all were menstruating at the time of their scan, none of the women were on oral contraceptives and none of the subjects were taking any type of hormone supplement. All subjects had been selected at random, from a previous off-line study of sex differences in cognitive abilities in which subjects completed the same battery of tests. All subjects who participated in the study provided signed consent, approved by the Institute of Psychiatry and Maudsley Hospital Ethical (Research) Committee. Subjects received £20 each for their participation.

5.3.2 Experimental Paradigms

5.3.2.1 Mental Rotation

This computerized three-dimensional block design consists of six control and six experimental conditions presented in a randomised order. Each condition lasts 30 seconds, with a TR of 3s, and is separated from the next condition by a rest period of 30 seconds, during which time a white cross is displayed on the screen. In every condition, 10 pairs of three-dimensional shapes are presented, and the participant indicates whether the two shapes in each pair are identical (same) or mirror images (different). In the control conditions, the two shapes are in the same angle of rotation and in the experimental conditions, they are not (see figure 5.1). Images are presented at 10 different angles of rotation, 0° to 180°, with half being identical and half mirror images. In total, 120 stimulus pairs are presented to the subject and the task lasts 12 minutes. Participants respond using a button box and accuracy and reaction times are recorded by computer.

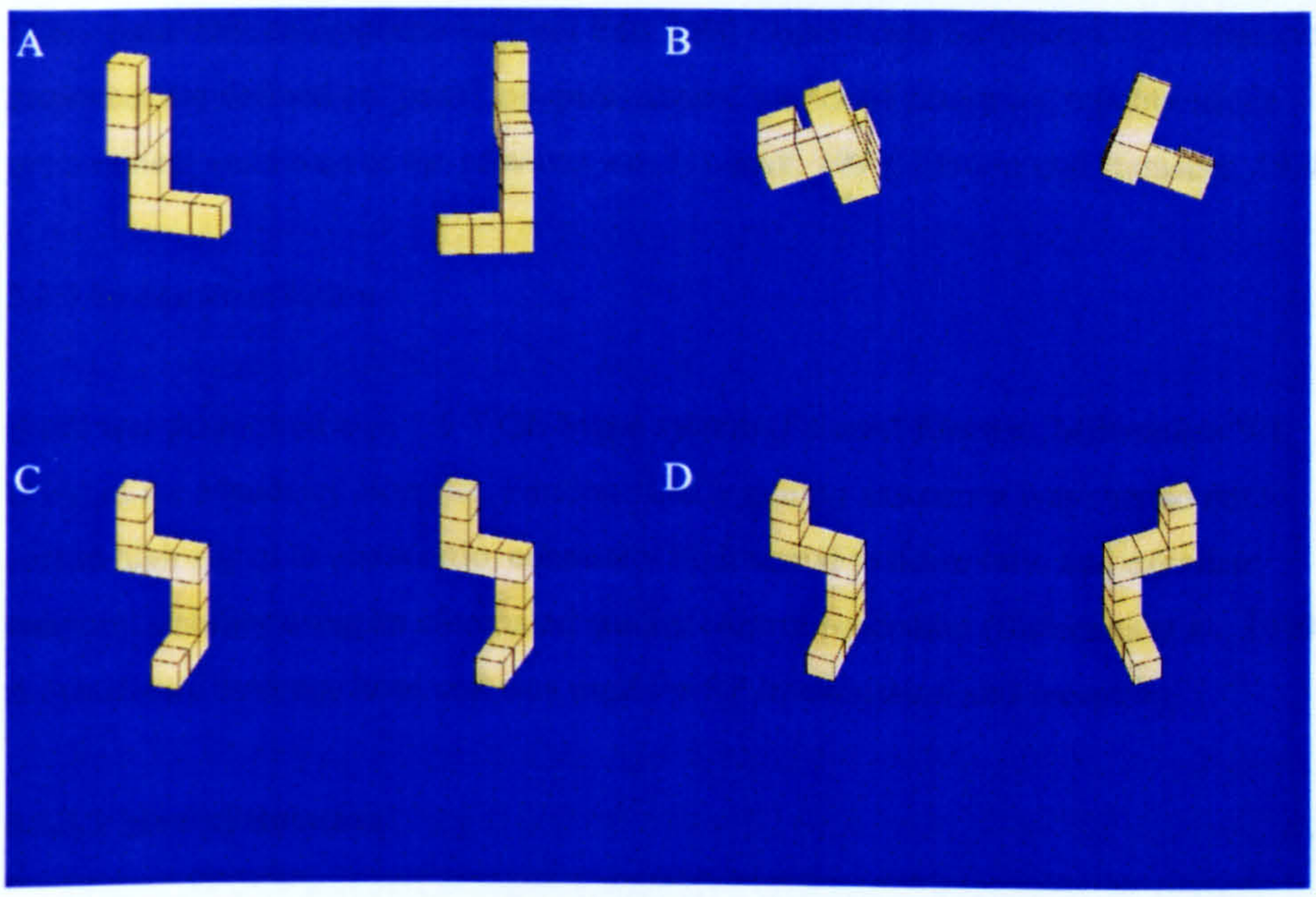


Figure 5.1. The top two images (A and B) are examples of the experimental condition. A: the right hand image is a rotated version of the left-hand image, so the response would be 'same'. B: the right-hand image is a rotated and mirror version of the left hand image, so response would be 'different'. The two images at the bottom C and D are examples of trials in the control conditions. C: the two images are identical (same). D: the two images are mirror versions of one another (different).

5.3.2.2 Verbal Fluency

This block design task involves generating as many words as possible beginning with a certain letter (F, A, S, P, R, W). The task consists of a control condition and an experimental condition, each lasting 50 seconds with 10 presentations of a given letter per experimental block. In total, the task lasts 10 minutes and 20 seconds. In the experimental condition, the subjects are cued by an auditory presentation of a letter (F, A, S, P, R, W) every 5 seconds (interstimulus interval; ISI), in which time they have to generate a word beginning with that letter, and to say that word aloud. During the control condition, the subjects are cued by an auditory presentation of the word "REST" every 5 seconds and they have say that word out aloud every time it is heard. The experimental condition is alternated with the control condition. Verbal responses are recorded via a

MRI-compatible microphone on Cool Edit 2000 (Syntrillium Software Corp.). Incorrect responses are defined as "pass", peoples' names, names of countries, repetitions, or grammatical variations of the previous word (Lezak, 1995; Benton and Hamsher, 1978).

5.3.3 Image acquisition

fMRI was performed on a 1.5 T GE Signa system (General Electric, Milwaukee WI, USA) at the Maudsley Hospital, London. Daily quality assurance was carried out to ensure high signal to ghost ratio, consistent high signal to noise ratio and excellent temporal stability using an automated quality control procedure (Simmons et al., 1999). A quadrature birdcage head coil was used for RF transmission and reception.

5.3.3.1 Mental Rotation

In each of 16 near-axial non-contiguous planes parallel to the inter-commissural (AC-PC) plane, 220 T_2*-weighted MR images depicting blood-oxygenation-level-dependent contrast (Ogawa et al., 1980) were acquired over the 12-minute experiment with echo time (TE) = 30 ms, repetition time (TR) = 3 s, in-plane resolution = 3.1 mm, slice thickness = 7.0 mm, interslice gap = 0.7 mm.

5.3.3.2 Verbal Fluency

For the verbal fluency task 124 T_2*-weighted MR images depicting BOLD contrast (Ogawa et al., 1980) were acquired over the 10-minute, 20 s experiment with echo time (TE) = 50 ms, repetition time (TR) = 5 s, in-plane resolution = 3.1 mm, slice thickness = 7.0 mm, interslice gap = 0.7 mm.

For both tasks head movement was minimised by foam padding within the head coil and a restraining band across the forehead.

5.3.4 General Procedure

Subjects were told that the purpose of the study was to investigate the neural correlates of performance on the mental rotation and verbal fluency tasks. The subjects were given instructions on the task before they were scanned. Women were scanned during the low estrogen phase of their menstrual cycle in order to control the role of estrogen on task performance. All subjects were scanned in the afternoon, when testosterone in men is known to be at its lowest (Dabbs, 1993).

5.4 Data Analysis

5.4.1 Behavioural Measures

Behavioural performance was assessed as percentage of correct responses (accuracy) and the time (in ms) taken to respond (reaction time RT) for correct responses (latency) on the mental rotation and verbal fluency tasks. A 2 (condition: experimental, control) x 2 (men, women) Analysis of Variance (ANOVA) was carried out to examine for any sex differences on task performance on the mental rotation task. For the verbal fluency, a one – way ANOVA was conducted to examine any sex differences for the total number of words generated.

5.4.2 Image Pre-Processing.

Image analysis was performed using statistical parametric mapping (SPM99; http://www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB 5.3 (Mathworks Inc., Natiek, MA, USA). For each subject, the 220 for the mental rotation and 124 for the verbal fluency volume functional time series was motion corrected (Friston et al., 1996a) transformed into stereotactic space using linear and non-linear affine transformations, spatially smoothed with a 7mm FWHM Gaussian filter and band pass filter.

5.4.3 FMRI Models.

5.4.3.1 Mental Rotation.

The data were analysed using random effect general linear models. This study examined activations (and de-activations) in men and women using a separate fixed effect model for each group, with a stringent statistical threshold, and examined differences between the groups using a random effect model within regions of interest at a more lenient threshold. Significance was assessed using a correction for multiple comparisons at the cluster level (P <0.05 corrected as described in Friston et al., 1996). The random effect analysis was performed on the parameter estimate images for each subject, derived from the random effect model, using a two-sample t-test to compare the groups.

5.4.3.2 Verbal Fluency.

The first four slices of the verbal fluency task were dummy images acquired before data acquisition and were therefore excluded from the analysis. A similar procedure to that described above for the mental rotation was employed for the verbal fluency task.

5.4.3.3 Sex differences in number of voxels activated

A series of t-tests were conducted to examine for sex differences in the significant number of voxels activated at the individual level for all subjects for the mental rotation and verbal fluency tasks. All analyses were performed by SPSS windows (version 11).

5.4.3.4 Activation in Relation to Sex Effects

In order to see whether there were any differences in activation between the 6 best performers and the 6 worst performers on the mental rotation and verbal fluency tasks, a between subject t-test was used. Significance was assessed using a correction for multiple comparisons at the cluster level (P <0.05 corrected). Based on the significant areas activated during this analysis, small volume corrections were made using a 5mm

sphere on the co-ordinates of interest. Men were compared to women for the mental rotation and women were compared to men for the verbal fluency task to examine whether differences existed between the sexes in these regions of interest ($P < 0.05$).

5.5 Results

5.5.1 Behavioural Measures

5.5.1.1 Mental Rotation

There was a significant sex difference ($F(1,17) = 7.26$; $p = .01$) favouring men on the mental rotation task. The significant two-way interaction between condition and sex ($F(1,17) = 29.22$; $p=.00$) revealed that as expected, the sex difference for response accuracy was present only in the experimental conditions and no sex differences were observed for the control conditions. A sex difference in response latency was also observed ($F(1,17) = 16.03$; $p =.00$), with men responding faster than women in general during the control condition (see table 5.1). There were no other significant interactions for the task.

Table 5.1

Means (standard deviation) for accuracy and response latency for the mental rotation and verbal fluency tasks for men and women

	Men	Women	t- value df (17)	p-value (2-tailed)
Mental Rotation				
Experimental	47.22 (4.32)	36.30 (4.57)	5.33	.00
Control	55.11 (4.93)	56.70 (4.29)	.750	.46
Experimental RT	2.82 (.31)	3.10 (.42)	1.64	.11
Control RT	2.67 (.48)	3.27 (.34)	3.11	.00
Phonological fluency				
Total Number of words generated	46.88 (4.93)	52.60 (5.75)	2.30	.03
Total Reaction Time	322.02(14.65)	319.71 (21.52)	.269	.79

5.5.1.2 Verbal Fluency

There was a significant sex difference favouring women ($F(1,18) = 5.324$, $p = .034$) on the number of words generated on the verbal fluency task, and no sex differences were found for response latency ($p > 0.05$) on the task.

5.5.2 FMRI

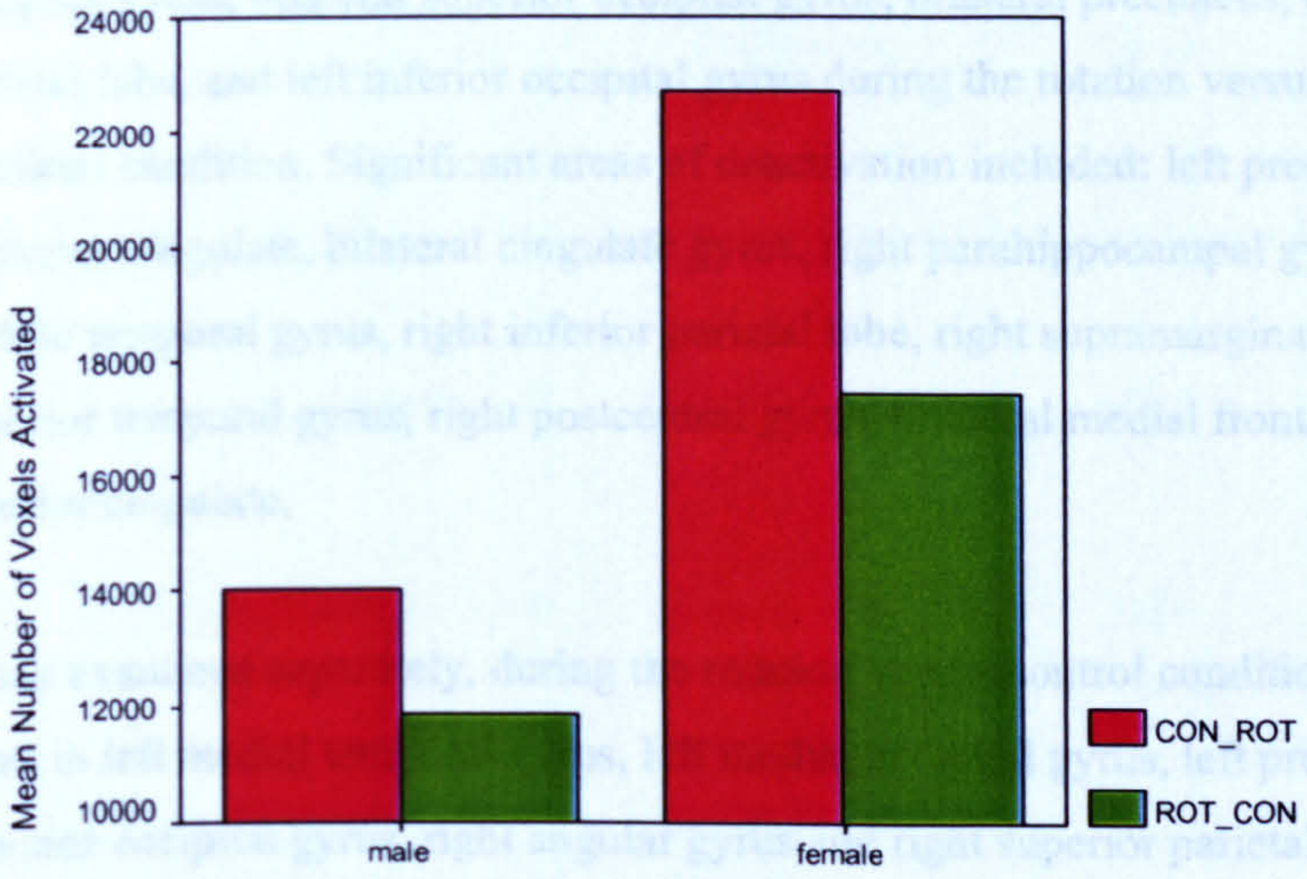
5.5.2.1 Sex differences in number of voxels activated

Overall, there was a sex difference in the number of voxels activated and deactivated for all the conditions of the mental rotation task; rotation compared with control condition ($t(17) = 2.483$, $P = .024$) and control compared with rotation condition ($t(17) = 2.231$, $P = .039$). For the verbal fluency task, women activated more voxels compared with men on the letter compared with the rest condition ($t(17) = 2.273$, $P = .036$). There were no sex

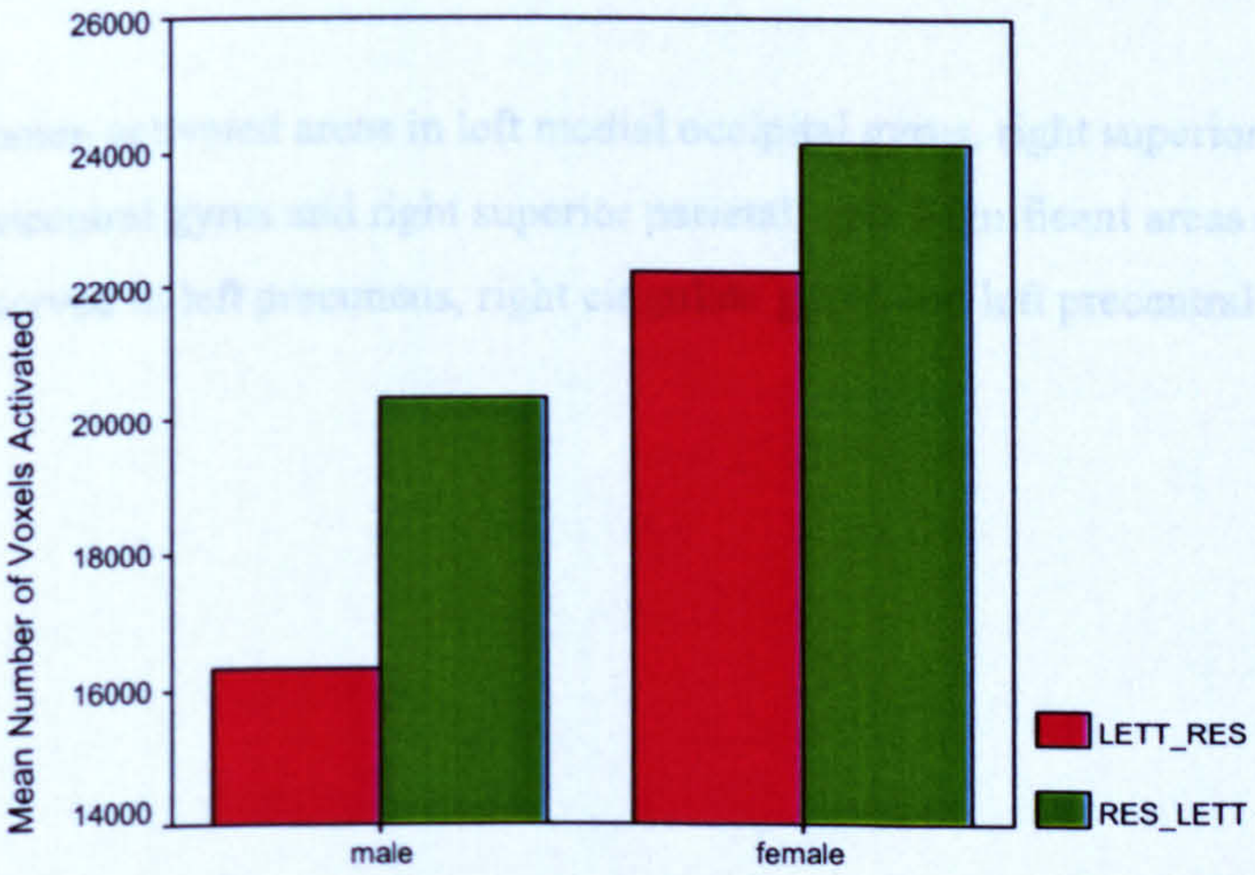
differences for the rest compared with letter conditions ($p > 0.05$) (see figure 5.2 a and b).

Figure 5.2 Bar graph showing the mean number of voxels activated for the (a) mental rotation task and, (b) verbal fluency task in men and women

a



b



5.5.3 FMRI Areas Of Activation In Men And Women

5.5.3.1 Mental Rotation

Overall, men and women activated areas in bilateral medial temporal gyrus, left medial occipital gyrus, bilateral superior occipital gyrus, bilateral precuneus, bilateral superior parietal lobe, and left inferior occipital gyrus during the rotation versus the control (no rotation) condition. Significant areas of deactivation included: left precuneus, bilateral posterior cingulate, bilateral cingulate gyrus, right parahippocampal gyrus, bilateral middle temporal gyrus, right inferior parietal lobe, right supramarginal gyrus, bilateral superior temporal gyrus, right postcentral gyrus, bilateral medial frontal gyrus, right anterior cingulate,

When examined separately, during the rotation versus control condition men activated areas in left medial temporal gyrus, left medial occipital gyrus, left precuneus, right superior occipital gyrus, right angular gyrus and right superior parietal lobe. Significant deactivation during this condition was observed in bilateral medial frontal gyrus, right anterior cingulate, right superior temporal gyrus, right supramarginal gyrus, right inferior parietal lobe, and left medial temporal gyrus.

Women activated areas in left medial occipital gyrus, right superior occipital gyrus, right postcentral gyrus and right superior parietal lobe. Significant areas of deactivation were observed in left precuneus, right cingulate gyrus and left precentral gyrus.

Table 5.2: Brain regions showing a significant change in BOLD response (random effect model corrected for multiple comparisons at the cluster level, $P < 0.01$) during the mental rotation task in healthy men (2a) and women (2b).

2a:

Men						
Brain region	Brodmann Area	Talaraich* Coordinates *(in mm)*	Side	Number of Voxels	T	*P*
Rotation > Rest		x y z				
Superior temporal gyrus	21	44 -20 -6	Right	22925	13.97	0.00
		0 -38 42			12.25	
		50 -10 -2			12.21	
Medial frontal gyrus	8	-22 26 38	Left	7328	12.40	0.00
		-2 18 8			8.07	
		-36 12 42			7.43	
Superior temporal gyrus	39	54 -60 28	Right	1112	12.26	0.00
Inferior parietal lobe	40	52 -58 38			9.83	
Supramarginal gyrus	40	60 -50 32			9.56	

Control > Rest								
Lingual gyrus	18	14	-88	-10	Right	11319	22.05	0.00
	18	-16	-86	0	Left		16.82	
Superior parietal lobe	7	32	-52	52	Right		16.35	
Rotation > Control								
Medial temporal gyrus	19	-34	-76	22	Left	1100	11.78	0.00
Medial occipital gyrus	18	-32	–82	2			5.27	
Precuneus	19	-26	-74	34			5.19	
Superior occipital gyrus	19	34	-70	22	Right	777	7.29	0.04
Angular gyrus	39	32	-62	34			5.70	
Superior parietal lobe	7	26	-54	62			4.54	
Control > Rotation								
Medial frontal gyrus	10	-2	60	16	Left	755	10.40	0.05
		8	58	16	Right		6.74	
Anterior cingulate	32	14	44	2			5.75	
Superior temporal gyrus	22	52	-40	12	Right	7540	9.14	0.00
Supramarginal gyrus	40	54	-52	18			8.80	
Inferior parietal lobe	40	66	-38	22			8.80	
Medial temporal gyrus	39	-44	-58	24	Left	2019	8.52	0.00
Temporal gyrus	41	-32	-34	12			5.38	
Medial temporal gyrus	21	-60	-36	0			5.28	

*Talairach and Tournoux (1988).

2b:

Women						
Brain region	Brodmann Area	Talaraich* Coordinates *(in mm)*	Side	Number of Voxels	T	*P*
Rotation > Rest		*x y z*				
Superior frontal gyrus	6	16 -12 60	Right	51371	36.99	0.00
Medial frontal gyrus	8	-20 34 40	Left		20.31	
Cingulate Gyrus	31	-12 -44 44			19.85	
Control > Rest						
Fusiform gyrus	19	-32 -78 -12	Left	17846	14.38	0.00
Lingual gyrus	17	18 -88 2	Right		14.28	
Postcentral gyrus	40	-46 -28 44	Left		12.83	
Inferior frontal gyrus	9	46 12 22	Right	1275	9.76	0.00
Medial frontal gyrus	46	54 32 14			7.43	
	10	34 58 -8			7.28	

Rotation > Control							
Medial occipital gyrus	19	-28	-78	12	Left	3308	11.71	0.00
		-38	-78	10			11.13	
		-34	-78	-2			9.15	
Superior occipital gyrus	19	38	-74	22	Right	2561	7.12	0.00
Postcentral gyrus	7	12	-52	62			6.43	
Superior parietal lobe	7	16	-58	58			6.13	
Control > Rotation							
Precuneus	31	-12	-48	34	Left	18392	13.81	0.00
Cingulate gyrus	31	4	-28	40	Right		12.69	
Precentral gyrus	4	-52	-10	28	Left		12.32	

5.5.3.2 Verbal Fluency

During the letter compared with rest condition, men and women activated bilateral superior frontal gyrus, right cingulate gyrus, bilateral middle frontal gyrus, left insula, bilateral inferior frontal gyrus, anterior cingulate, thalamus, right lingual gyrus. Significant deactivations on this condition were seen in bilateral precuneus, left inferior parietal lobe, right superior frontal gyrus, right medial frontal gyrus, left parahippocampal gyrus, right cingulate gyrus, and left superior temporal gyrus.

In men, activation was found in bilateral superior frontal gyrus, right cingulate gyrus, left precentral gyrus, left inferior frontal gyrus, left medial frontal gyrus, right thalamus, left parahippocampal gyrus and bilateral lingual gyrus during the letter compared with rest condition. Deactivations were observed in right precuneus, left cingulate gyrus, right posterior cingulate, left superior frontal gyrus, right medial frontal gyrus, right anterior cingulate, right medial temporal gyrus, bilateral superior temporal gyrus, right medial occipital gyrus, left parahippocampal gyrus, left fusiform gyrus and left inferior parietal lobe during this condition.

In women activation was found in bilateral inferior frontal gyrus and caudate during the letter compared with rest condition. Significant areas of deactivation were observed in right cingulate gyrus, bilateral precuneus, left superior temporal gyrus, left inferior parietal lobe and right postcentral gyrus.

5.5.3.3 Sex Differences In Areas Of Activation

There were no significant differences in activation between men and women on the mental rotation or verbal fluency tasks. This was also true when testing for voxels more active in men than in women; on the two tasks, the region of interest was defined by the fixed effect activations in the male group. Conversely, when testing for voxels more active in women than in men on the two tasks, the region of interest was defined by the fixed effect activations in the female group ($P > 0.05$).

Table 5.3 a and b: Brain regions showing a significant change in BOLD response (random effect model corrected for multiple comparisons at the cluster level, $P < 0.01$) during the overt verbal fluency task in healthy men (5.3a) and women (5.3b).

(a)

Men						
Brain region	Brodmann Area	Talaraich* Coordinates *(in mm)*	Side	Number of Voxels	T	*P*
Letter > Rest		*x y z*				
Superior frontal gyrus	6	-2 14 54	Left	1049	25.79	0.01
		10 14 58	Right		6.31	
Cingulate gyrus	32	6 28 30			5.27	
Precentral gyrus	6	-50 0 48	Left	2207	15.12	0.00
Middle frontal gyrus	9	-52 8 34			10.11	
Inferior frontal gyrus	45	-52 14 20			9.58	
Thalamus		6 -32 8	Right	1230	8.45	0.00
Parahippocampal gyrus	30	-4 -36 0	Left		6.06	
Thalamus		2 -16 6	Right		5.75	
Lingual gyrus	18	-4 -72 -10	Left	1035	7.73	0.01
Lingual gyrus		6 -70 -8	Right		6.21	

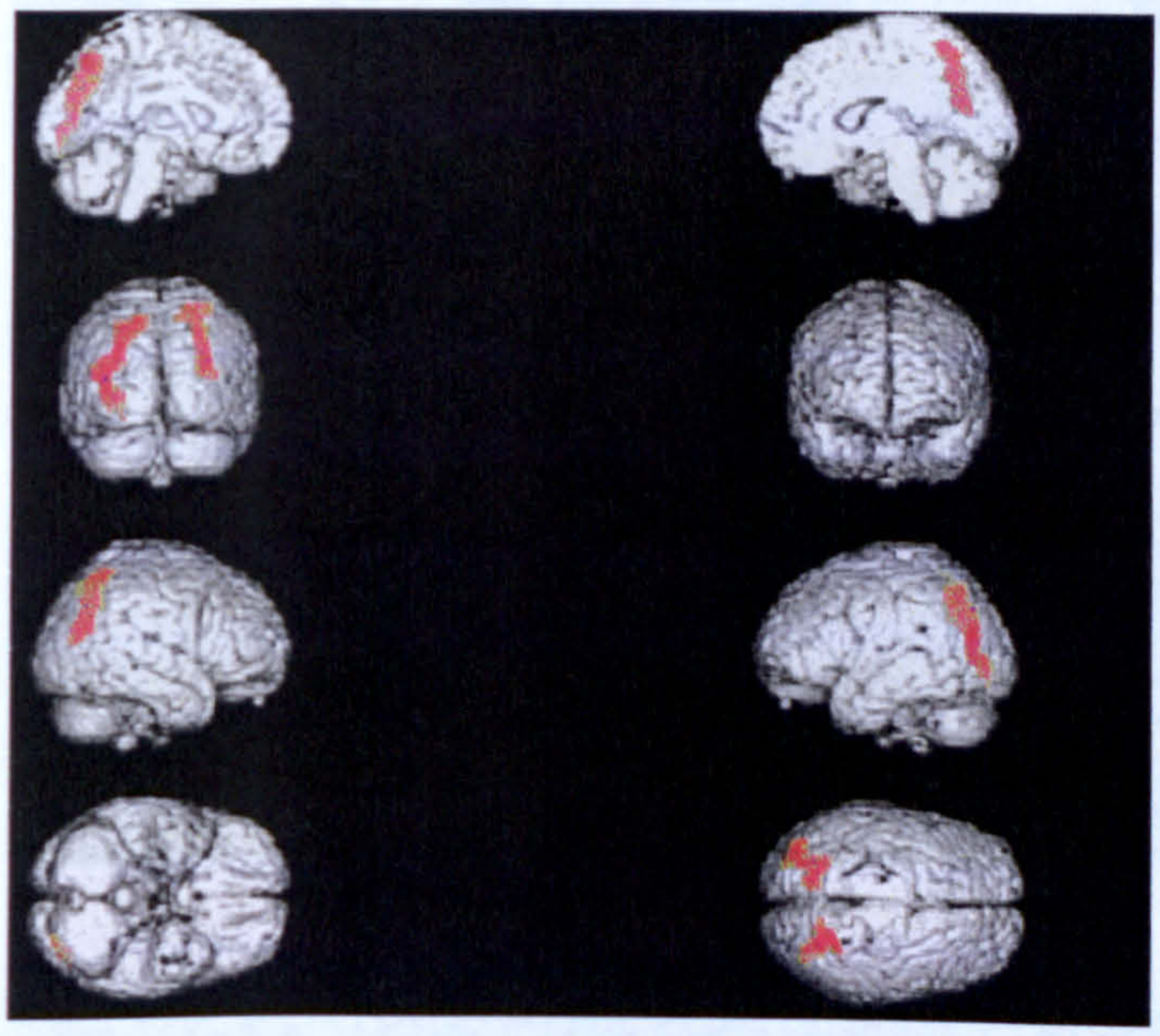
Rest > Letter								
Precuneus	7	0	-58	30	Right	7005	15.58	0.00
Cingulate gyrus	31	-8	-48	38	Left		10.97	
Posterior Cingulate	29	10	-48	16	Right		10.41	
Superior frontal gyrus	10	-16	56	-4	Left	1680	10.42	0.00
Medial frontal gyrus	10	8	62	6	Right		7.40	
Anterior cingulated	24	2	32	6			6.40	
Medial Temporal gyrus	39	56	-58	8	Right	2277	10.14	0.00
Superior temporal gyrus	39	46	-52	16			9.55	
Medial occipital gyrus	19	42	-74	2			7.88	
Parahippocampal gyrus	36	-18	-32	-16	Left	2256	8.45	0.00
Parahippocampal gyrus	27	-22	-28	-4			6.58	
Fusiform gyrus	20	-30	-38	-16			6.53	
Inferior parietal lobe	40	–52	-58	38	Left	1282	8.35	0.00
Inferior parietal lobe	39	-42	-66	42			7.70	
Superior temporal gyrus	39	-56	-56	28			6.33	

(b)

Women						
Brain region	Brodmann Area	Talaraich* Coordinates *(in mm)*	Side	Number of Voxels	T	*P*
Letter > Rest		*x y z*				
Inferior frontal gyrus	47	-42 18 -6	Left	18696	9.32	0.00
Caudate		-12 4 20			8.67	
Inferior frontal gyrus	47	44 18 -12	Right		8.53	
Rest > Letter						
Cingulate gyrus	31	8 -56 30	Right	4984	20.96	0.00
Precuneus	31	-6 -48 32	Left		15.41	
Precuneus	7	10 -48 38	Right		10.67	
Superior temporal gyrus	39	-44 -58 32	Left	871	8.30	0.04
Inferior parietal lobe	39	-40 -64 38			6.78	
Postcentral gyrus	40	62 -18 18	Right	975	7.39	0.02
Postcentral gyrus	43	52 -18 16			6.98	
Precentral gyrus	6	54 -6 8			5.06	

Figure 5.3 a and b show areas of activation during the Rotation compared with the Control condition in (a) men and (b) women.

(a)



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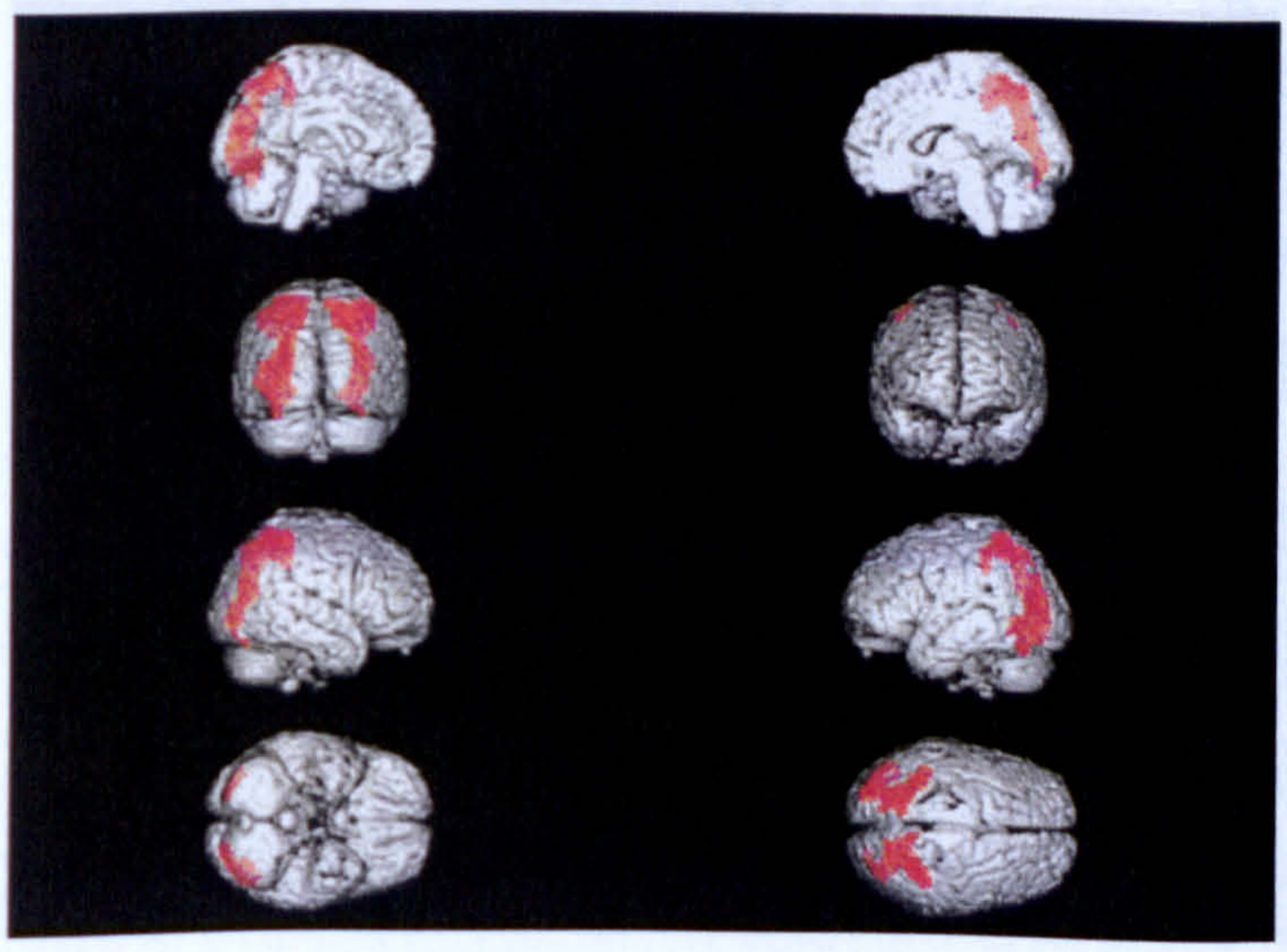
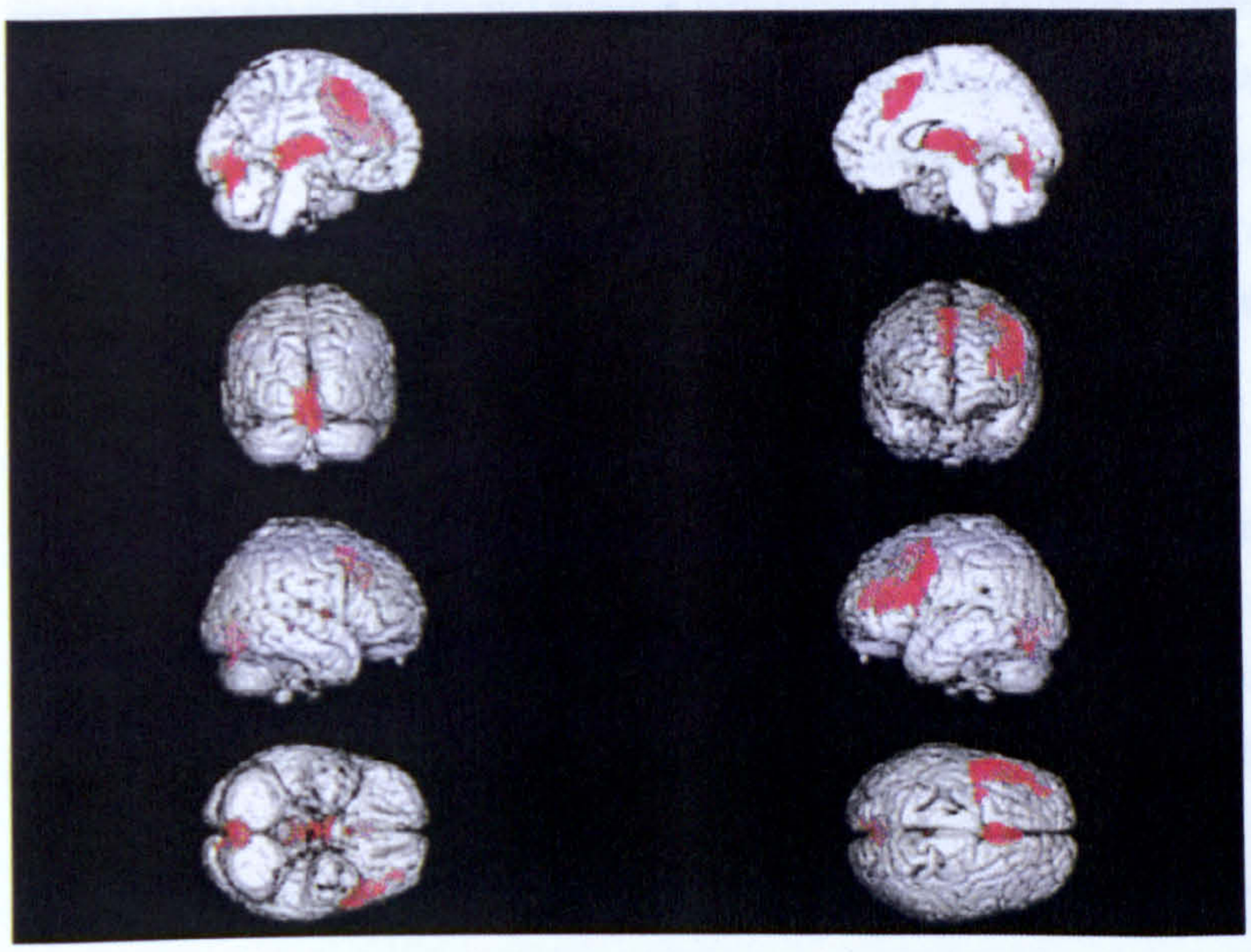
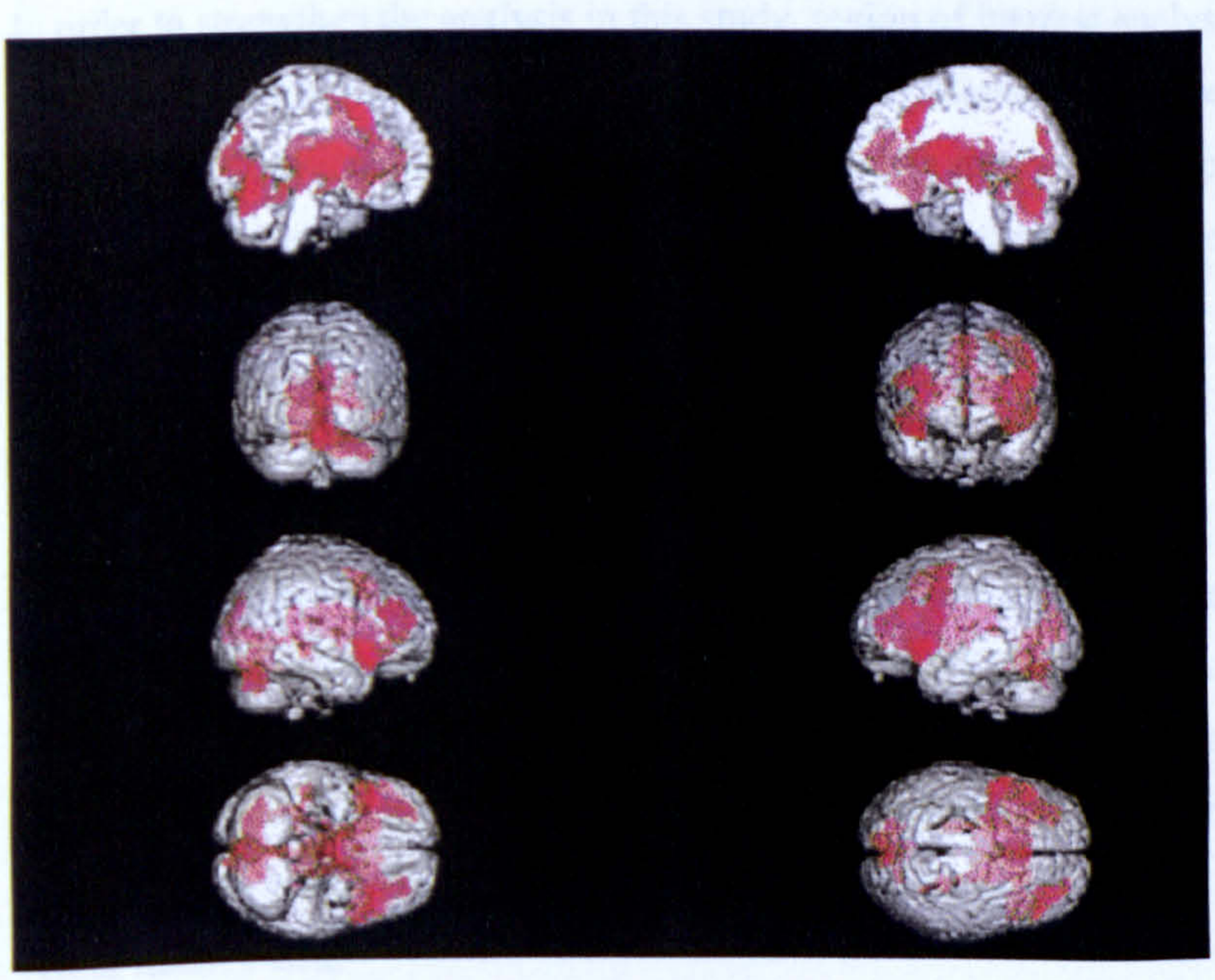


Figure 5.4 a and b show areas of activation during the Letter compared with Rest condition in (a) men and (b) women.

a



b



5.5.3.4 Performance Related Activation

The analyses of the 6 best performers (men or women) with the six worse performers (men or women) on the mental rotation task revealed a significant difference in activation in left fusiform gyrus (BA19), left middle temporal gyrus (BA19) and left inferior parietal lobe (BA40), whereas the worse (compared to the best) performers activated the parahippocampal gyrus on the rotation compared with the control condition ($P < 0.05$). There were no other significant areas of activation between the best and worst performers on any conditions of the mental rotation task ($P > 0.05$).

For the verbal fluency task, there was significant difference in activation in the hippocampus, when the 6 best performers were compared with the 6 worst performers on the letter compared to the rest condition ($P < 0.5$). No other significant areas of activation were found on this condition or on the rest compared with the letter condition ($P > 0.05$).

5.5.3.5 Volume of Interest Analysis

In order to strengthen the analysis in this study, region of interest analyses based on the significant substrates of activation in the performance related analysis revealed no significant differences in these areas of activation when men were compared with women on the mental rotation task and women were compared to men on the verbal fluency task ($P > 0.05$).

5.6 Discussion

The present study was designed to measure neural activation in men and women during performance on a 3-D mental rotation and an overt verbal fluency task using a compressed sequence design. Consistent with our hypothesis, behaviourally, men outperformed women on the percentage of correct responses on the mental rotation condition, and women outperformed men on the total number of words generated on the verbal fluency task.

As expected, at the neural level in women, activation was observed in right superior parietal lobe during the rotation compared with the control condition. Other areas of activation on this condition included, left medial occipital gyrus, right superior occipital gyrus and right postcentral gyrus during the rotation compared with the control condition. Men activated similar areas in right superior parietal lobe, right superior occipital gyrus and left medial occipital gyrus, with additional activation in left medial temporal gyrus and left precuneus during this condition.

The present study did not find any sex differences in neural activation on the mental rotation task, which is consistent with previous studies that found no differences in brain activation with differing behavioural performance between the sexes (Untterainer et al., 2000; Dietrich et al., 2001), whereas some studies have reported sex differences in brain activation in the absence of group differences in behavioural performance (Thomsen et al., 2000; Jordon et al., 2002). The findings showed that men and women were activating similar brain areas for the mental rotation task, although women were performing differently (making more response errors), which may be a reason why sex differences were not found at the neural level. Also, women in general were found to activate more voxels in both tasks during the low estrogen phase of the menstrual cycle.

Consistent with previous studies, activation was found in the superior parietal lobe (Thomsen et al., 2000; Jordon et al., 2002; Harris et al., 2000; Cohen et al., 1996; Tagaris et al., 1997) in men and women, although men have been suggested to show more right lateralized activation and women more bilateral activation during the mental rotation task (Gur et al., 2000). The present study, however, found that both men and women activated right superior parietal lobe, and did not find bilateral activation of the superior parietal lobe in women. It has been suggested that bilateral activation of the parietal areas may be a result of the increasing demands of the task (Corballis, 1997), though varying levels of difficulty was not examined in the present study. Furthermore, it has been proposed that bilateral activation of the parietal lobe is not related to mental rotation processes per se, but to subserving task performance (Harris et al., 2000; Alivisatos and Petrides, 1997; e.g. the control of eye movements, Berman et al., 1999, and visual spatial

orienting, Nobre et al., 2000). Activation found in the left medial and right superior occipital gyrus in both men and women have previously been found to be related to the percentage of errors made on the 3-D mental rotation task (Tagaris et al., 1997).

An examination of differences between good and poor performers on the mental rotation task, revealed additional activation in left inferior parietal lobe, left fusiform gyrus and left middle temporal gyrus on the rotation compared with the control condition, whereas the parahippocampal gyrus was activated when poor performers were compared to the good performers. The activation of the left inferior parietal lobe in good performers may suggest that bilateral activation (of parietal areas) may be related to better performance on the mental rotation task. Our findings may suggest that optimal performance on the mental rotation task may require the recruitment of bilateral parietal areas, as well as areas as the left middle temporal gyrus and fusiform gyrus. Activation of the middle temporal gyrus has been associated with covert visuospatial attentional shifts in a healthy group of subjects (Kim et al., 1999; Gitelman, 1999), although this finding would need to be replicated in relation to good mental rotation performance.

Dietrich et al. (2001) found similar areas of activation for the mental rotation task in men and women, and they did not find any sex differences on the mental rotation task, even when taking into account fluctuations in hormone levels during different phases of the menstrual cycle (Dietrich et al., 2001). Their study reported an increase in hemodynamic response in women when tested during the high estrogen phase of the cycle during performance on the mental rotation task, whereas the results of the present study differed from those of Dietrich et al. In fact, as mentioned previously, overall increased activation in women was found compared with men during performance on the mental rotation task. One explanation for this discrepant finding could be related to an increased effort made by women during the mental rotation task.

In the verbal fluency task, consistent with the hypothesis of the current study, women activated bilateral inferior frontal gyrus and left caudate during the letter compared with rest comparison. However, men activated a broader network of areas including left

inferior frontal gyrus, bilateral superior frontal gyrus, right cingulate gyrus, left precentral gyrus, left medial frontal gyrus, right thalamus, left parahippocampal gyrus and bilateral lingual gyrus.

The activation observed in the inferior frontal gyrus during the verbal fluency is consistent with previous studies that have investigated language abilities (Fiez, 1997; Wise et al., 1991) and verbal fluency (Yetkin et al., 1995; Phelps et al., 1997; Frith et al., 1991; Paulesu et al., 1997; Schlosser et al., 1998; Friedman et al., 1998; Hutchinson et al., 1999; Lurito et al., 2000; Fu et al., 2002). Frith et al. (1991) suggested that activation in this area is attributed to the selection of responses at will (i.e. generating a response), although others have suggested that the inferior frontal gyrus is related to the semantic processing of verbal stimuli (Kapur et al., 1994; Tulving et al., 1994).

Consistent with previous lateralization findings (Gur et al., 2000; Shaywitz et al., 1995), the current study found that performance on the verbal fluency task revealed more left lateralized activation in the inferior frontal gyrus in women and bilateral activation of this area in men, although this did not reach significance. In addition, in contrast to women, men activated more frontal areas (bilateral superior frontal gyrus, medial frontal gyrus). These areas have also been activated in previous verbal fluency studies using fMRI (Yetkin et al., 1995; Schlosser et al., 1998; Hutchinson et al., 1999). Activation of the left superior frontal gyrus has been associated with searching through memory for semantic associations (Phelps et al., 1997), which may also be related to searching for words beginning with a specified letter. Phelps et al. also found activation in the middle frontal gyrus and attributed this activation to the effortful search for words that was required in their 'generate' (thinking of a word beginning with a certain letter) condition of the verbal fluency task. Thus, a possible explanation for this additional activation in men in our study is that they may have need to recruit more frontal areas for better performance on this task. Alternatively, it may also open up the possibility that men are using a different strategy to women when performing this task.

Additional activation was also found in the thalamus, lingual, cingulate and parahippocampal gyri in men, and the caudate in women. Both the thalamus and caudate have been have been reported to be related to language processing (Johnson and Ojemann, 2000). Previous imaging studies have found that articulatory demands of the task were related to increased activation of the caudate and thalamus (Murphy et al., 1997). Thus, activation of the caudate in women and the thalamus in men in the present study may be related to factors of articulation and language processing (Murphy et al., 1997; Watkins et al., 1999).

The present study did not find any sex differences in neural activation for the verbal fluency task. This finding is consistent with those of Schlosser et al. (1998), who did not find any sex differences in a group of men and women during performance of a silent verbal fluency task. When comparing the 6 good performers with the 6 poor performing individuals the only difference was found in the hippocampus. This is a novel finding and would need to be replicated. Furthermore, like the mental rotation task, sex differences in neural activation may have been detectable if the current study included subjects that did not differ in behavioural performance.

A novel aspect of this study was the finding that overall, at the individual level, women activated significantly more voxels compared with men for the mental rotation task and the letter compared with the rest condition of the verbal fluency task during the low estrogen phase of the menstrual cycle. Although women activated a larger spatial extent, the areas activated by men and women did not differ significantly with differences in behavioural performance. Similar behavioural performance on these tasks may have revealed a smaller of different activation in magnitude in men and women. This finding is of interest and may highlight patterns of activation that are characteristic for women during performance on these tasks. Future studies should take this into account and a comparison of activation during the different phases of the menstrual cycle may shed more light into what constitutes a female-typical pattern of activation on these tasks.

One methodological point which should be considered in future studies is to take measure levels of estradiol, lutenizing hormone, follicle-stimulating hormones and progesterone to verify the cycle phase and to be sure that all the women are in the normal ranges for all hormones. Some subjects may have needed to be excluded because they may have had abnormal hormone levels or because they were not in the required phase of the menstrual cycle.

The present study showed behavioural sex differences favouring men on the mental rotation task and favouring women on the verbal fluency task. The absence of sex differences in neural activation suggest that men and women do not differ significantly in the brain areas used for these tasks when performing differently; however, equal performance by the two groups may elicit significant sex differences in brain activation, which will shed light on whether men and women differ in the neural resources used, as well as whether they use different cognitive strategies to perform these tasks.

Chapter 6: General Discussion

The primary aim of this thesis was to examine the differences between males and females in relation to neurocognitive functioning in healthy men and women and men and women with schizophrenia. It also looked at the role of organizational influences of endogenous levels gonadal hormones and gonadotropins to cognitive functioning in men and women. This was examined in three different studies. Study 1 investigated the organizational role of gonadal hormones in a healthy sample of men and women in relation to a sexually dimorphic cognitive battery comprising mental rotations, verbal fluency, cognitive inhibition and judgement of line orientation (with the N-back working memory task included for control purposes). Study 2 examined the relationship between gonadal hormones, cognitive functioning (attention, verbal abilities, memory, executive functioning, motor and speed of information processing) and symptomatology in a group of men and women with chronic schizophrenia. Study 3 investigated whether sex differences in behavioural performance on a sub-set of sexually dimorphic tasks (mental rotation and verbal fluency) reported in Study 1 translated to neural sex differences using functional MRI in a randomly selected sub-group of healthy men and women (from Study 1) whilst controlling for menstrual cycle phase (and thus controlling for estrogen levels).

The aims of the thesis were driven by the theory of neurohormonal sexual differentiation which proposes that gonadal hormones, in particular estradiol and testosterone during puberty, and across the menstrual cycle in women (activational effects) influence performance on certain cognitive tasks in both sexes and in sex-related cognitive deficits in schizophrenia.

The following is a summary of main findings reported in the present thesis:

<u>Study 1</u>

1. Sex differences favouring men on visuospatial tasks (mental rotation, JOLO) and favouring women on the verbal (category) fluency task were found.

2. Men performed better than women on the cognitive inhibition task (responding to numbers decreasing (backward counting) in numerical order).
3. A sex difference favouring women on the 0-Back condition and favouring men on the 1-back condition of the N-back task was observed.
4. Several relationships between gonadal hormones and gonadotropins were found in men and women. Specifically, these involved SHBG, FSH, LH and performance on the mental rotation, modified judgment of line orientation (MJOLO) and the cognitive inhibition tasks in women and FSH, LH and progesterone with performance on the cognitive inhibition task in men.

Study 2

1. No sex differences were found in performance on a standard neuropsychological battery between men and women with schizophrenia.
2. In the whole sample, high estrogen and older age was associated with low positive symptom scores.
3. Within gender: Cortisol predicted poor performance on the information-processing domain in men.

Study 3

1. At the behavioural level, men performed significantly better than women on the performance accuracy for the mental rotation task, whereas women generated more words than men on the verbal fluency task.
2. Similar areas of neural activation were found in men and women for the mental rotation and verbal fluency with differing behavioural performance.
3. No sex differences were found in brain activation during the mental rotation or verbal fluency tasks.
4. Women in general activated more voxels compared with men.

Study 1

The findings of sex differences favouring men on visuospatial tasks such as the mental rotation task and favouring women on the verbal fluency task are consistent with previous studies (Maccoby and Jacklin, 1974; Halpern, 1992, 1997, Voyer et al., 1995; Halpern, 1992,1997; Collaer and Hines, 1995; Kimura, 1999). A novel finding was the sex difference favouring men on the cognitive inhibition task, which was consistent with

the hypothesis proposed by Broverman et al (1968). This study is the first to have tested this hypothesis in a healthy group of men and women.

The sex difference favouring women on the 0-Back and favouring men on the 1-Back condition was another novel finding, and this is the first study to have reported this difference in a group of healthy men and women. The finding that women performed better than men on the 0-Back condition, which does not involve the use of memory processes, and of men performing better than women on the 1-back condition, which involves an inhibition component, lends further support for Broverman's (1968) hypothesis.

The effects sizes reported for the visuospatial tasks ranged from d = 0.75 – 1.04, the largest (1.04) being for mental rotation. These effect sizes for the spatial tasks are comparable with those reported in previous studies (Linn and Petersen, 1985; Collaer and Hines, 1995). This mitigates suggestions that computerized versions of mental rotation tasks might show smaller sex differences than paper and pencil versions (Voyer et al., 1995).

The effect size found for the letter (phonological) fluency (d = 0.23) task was small and for the category fluency (d = 0.61) task was moderate and consistent with previously reported effect sizes for letter fluency (d = 0.3) and category fluency (d = 0.5) (Acevedo et al., 2000; Hyde and Linn, 1988; Capitiani et al., 1999; Herlitz et al., 1997; Laws, 1999; Loonstra et al., 2001; Mann et al., 1990; Sumerall et al., 1997).

The results of the relationships between gonadal hormones and cognitive abilities are inconsistent with previously reported findings. No relationship between testosterone and spatial abilities in men is consistent with some previous studies (McKeever and Deyo, 1990; Gordon et al., 1986) but inconsistent with others (Janowsky et al., 1994; Christiansen, 1993; Christiansen and Knussmann, 1987), and no associations were found between verbal abilities and estrogen in women, which is consistent with the findings of

Gordon and Lee (1983) and inconsistent with some previous studies (Hampson, 1990a, 1990b; Silverman and Phillips, 1993) .

The findings with regard to cognitive inhibition and gonadal hormones and gonadotropins have never before been reported. Relationships of LH and FSH have been reported in relation to cognitive performance in previous studies (Gordon and Lee, 1986, 1993). The present findings were different to those reported in these previous studies and may be related to differences in methodologies. However, these findings still outline the importance of including these hormones when examining hormone-cognition relationships.

Only a few studies have reported positive relationships between testosterone and spatial ability and estrogen and verbal abilities, though in actual fact these relationships are far from clear. Many of these assumptions are based on findings from a small number of studies that have examined the relationship of endogenous levels of hormones in either men or women or in women during different phases of the menstrual cycle (see chapter 1). The inconsistencies in the literature are due to the diverse methodologies used such as: (1) time of day of testing, (2) taking blood or saliva measures of hormones (3) different assay techniques used to measure hormone levels (4) restricting hormone measures to either estrogen, or testosterone (5) the use of tasks that do not measure sex differences and, (6) absence of hormone measures to verify cycle phases.

Study 1 has several robust features that reinforce the validity of the results. Firstly, the time of day of testing, and blood sample collection, was the same for all subjects (9.00 am – 10.30 am). Secondly, it employs a range of cognitive tasks previously shown to elicit modest to large sex differences. Thirdly, a wide range of hormone measures were taken in order to both verify cycle phase in women and to examine the associations between hormones other than estrogen and testosterone to cognitive performance.

Study 2

It is important to make clear that at the outset, the aim of this thesis was to look at both sex dimorphic cognitive abilities (as described in chapter 3) and a general neurocognitive

battery in patients with schizophrenia (conducted in chapter 4). However, due to the fact that patients had to complete a 2-21/2 hour neurocognitive battery and have a clinical assessement not all patients consented to completing the sex dimorphic battery. Therefore, because of small sample sizes, data on the sex differences battery was not included in the thesis.

No cognitive sex differences were found in a wide range of cognitive tests in schizophrenia. These findings are consistent with several other studies (Hoff et al., 1992; Andia et al., 1995;Goldberg et al., 1995) yet inconsistent with others (Haas et al., 1991; Goldstein et al., 1994, 1995; Hoff et al., 1995; Hoff et al., 1998; Seidman et al., 1996; Perlick et al., 1992; Lewine et al., 1996).

Much of the discrepancy in findings in the literature relates to different methodologies used, such as: (1) testing different patient samples (chronic and first episode) of men and women (2) using different cognitive measures across studies (3) patients differ in their dosage and medication type 4) insufficient sample size to detect any sex-effects 5) failure to account for age at onset. The present investigation tested a group of men and women with chronic schizophrenia and controlled for age of onset of the illness, medication type (all subjects were on conventional antipsychotic medication) and dosages. All subjects were tested at the same time of day. Furthermore, composite scores were calculated for each cognitive domain based on previously used cognitive measures.

This study did not administer a sex dimorphic battery to the patients with schizophrenia because neurocognitive deficits in schizophrenia are known to be more widespread, and the aim of this study was to examine whether hormones related to any aspect of these cognitive functions.

An important finding of this study was that higher levels of endogenous estrogen were associated with lower scores on the positive symptom scale of the positive and negative symptom scale (PANSS), which is consistent with previous studies (Kulkarni et al.,

1996, 2001; Thompson et al., 2000) that tested younger women of childbearing age, in the acute phase of their illness. In contrast to these, the present findings were demonstrated in an older sample of chronic schizophrenia. This is also the first study to report this relationship in both men and women with chronic schizophrenia.

These findings also reinforce the evidence favouring the antidopaminergic properties of estrogen (Hafner et al., 1991; Hafner et al., 1993, Hafner, 2003), which suggests that estrogen reduces dopamine concentration in the striatum and modulates sensitivity as well as the number of dopamine receptors (Koller et al., 1980; Foreman and Porter, 1980; Dupond et al., 1981; Bedard et al., 1984; McEwen and Woolley, 1994; Di Paolo, 1994).

Study 2 also found that higher levels of cortisol were related to poor performance on the speed of information processing domain in men. This finding is of importance and reinforces previous findings of dysregulation in cortisol levels in schizophrenia and its relation to frontal task functioning (Walder et al., 2000).

Study 2 found higher levels of progesterone related to poor performance on the spatial memory domain, and higher levels of testosterone to better performance whilst controlling for age. This is a new finding in men and women with chronic schizophrenia. These findings support the suggestion that progesterone (and to some extent testosterone), like estrogen has psychotropic properties, which may relate to cognitive performance (see chapter 4). Hoff et al., (2001) found that average levels of estrogen were related to better cognitive functioning in the language, executive functioning, verbal memory, spatial memory, concentration/speed and perceptual speed domains, and average levels of progesterone were related to measures of spatial memory (composite measures of the Benton visual retention test; BVRT; Weschler memory scale). The authors tested early onset women with schizophrenia who were either taking oral contraceptives, on estrogen replacement therapy, or neither of these and restricted their hormone measures to estrogen and progesterone. The current investigation examined a wider range of hormones in a naturalistic environment, whereas Hoff et al.'s (20001) study involved artificially raised levels of gonadal hormones (exogenous administration),

as well as consisting of a sample of a severely ill group of early onset patients who would not be representative of women with schizophrenia as a whole. The finding of a relationship between testosterone and spatial memory was parallel to a previous study (Postma et al., 2000) that demonstrated improvements in aspects of object location memory after testosterone administration in healthy young women. The present investigation found this relationship in basal levels of testosterone in women with schizophrenia for the first time. This further supports the assumption that hormones other than estrogen can be associated with cognitive functioning in women.

Study 2 also found positive relationships between AOO and spatial memory and visuomotor performance in women. A negative relationship was found between AOO and motor performance in men, so that older AOO was related to making fewer taps on the finger tapping test. These findings suggest that factors other than sex hormones i.e. AOO can also be a good predictor of performance on cognitive tasks.

Robust features of study 2 were the examination of endogenous levels of a wide range of hormones in a sample of both men and women with schizophrenia. This allows for the verification of menstrual cycle phase, to detect any abnormalities in basal levels of stress, (cortisol, prolactin), gonadal hormones (estrogen, testosterone, progesterone) and gonadotropins (LH and FSH) in this study's sample of patients. These findings demonstrate that estrogen does have a beneficial role in reducing positive symptom scores and that the stress hormone cortisol is of importance in cognition in schizophrenia. However, the small sample size may have made it difficult to detect any other significant relationships between hormones and cognition.

In study 3, sex differences favouring men on performance accuracy for mental rotation task and favouring women on the verbal fluency task were found on line. However, in study 1, a sex difference favouring women was found on the category fluency and not the letter fluency test. Furthermore, the effect size for the letter fluency test was smaller than the category fluency. The letter fluency task administered in the behavioural study involved generating as many words with a given letter (F, A, S) in a minute, whereas the

task used in the fMRI scanner involved subjects generating 10 words, every 5 seconds from a given letter (F, A, S, P, R,W). The time that subjects are given to generate a word, coupled with the fact that subjects are in the scanner (which may have put them under pressure) may be a possible reason for finding a sex difference on this task.

Activation of the right superior parietal lobe found in men and women confirmed findings from previous studies (Thomsen et al., 2000; Jordon et al., 2002; Harris et al., 2000; Cohen et al., 1996; Tagaris et al., 1997) implicating the role of this region in mental rotation. The activation seen in the left inferior parietal lobe and middle temporal gyrus in good compared with poor performers suggest that optimal performance on this task requires bilateral parietal activation, which confirms Gur's (2000) bilateral advantage hypothesis.

The absence of sex differences in brain activation between the sexes on the mental rotation task is consistent with some studies that found no sex differences in brain activation with differing behavioural performance. (Untermainer et al., 2000; Dietrich et al., 2001). Some studies have reported sex differences in neural activation in the absence of between sex differences in behavioural performance (Thomsen et al., 2000; Jordon et al., 2002). In study 3, men and women were found to activate similar brain regions, with women making more response errors on the rotational component of the task. It is possible that if task difficulty was factored, so that men and women could be compared against the varying levels of difficulty (i.e. increases in angular disparity), the chances of detecting neural differences between men and women may have been greater. One study reported a positive association between task difficulty on mental rotations and strength of parietal activation (Tagaris et al., 1996), as well as bilateral parietal activation (Corballis, 1997). But there is no further information currently available on task strategy and neural activation.

Although no significant sex differences were found in neural activation to the verbal fluency test, activation of bilateral inferior frontal gyrus (IFG) in women and left IFG in men during the letter compared with the rest condition (although not reaching

significance) confirms previous lateralization findings (Gur et al., 2000; Shaywitz et al., 1995). More frontal (bilateral superior frontal gyrus, medial fontal gyrus) activation observed in men could suggest more cognitive effort made by men or could implicate a different strategy to perform the task compared with women, who did not show such activation.

The absence of neural sex differences on this task is consistent with findings from a study using a silent verbal fluency paradigm in the scanner (Schlosser et al., 1998). The current investigation is the first to examine sex differences in neural activation to a verbal fluency task using a compressed sequence design. Like the mental rotation task, equated behavioural performance on this task may have led to detectable neural sex differences. The precise relationship between the extent of cognitive effort and neural activation is unknown. It is not known whether bilateral activation of the IFG in females is due to their easy execution of tasks involving phonological and semantic processing, or because the two sexes are recruiting different strategies to perform the task.

A novel and interesting aspect of study 3 was the finding that women were activating a greater spatial extent compared to men for the mental rotation task and the letter compared with the rest condition of the verbal fluency task. However, they did not show any differential regional activation compared with men and there were no differences in behavioural performance. This finding is of interest because it may provide information of the patterns of brain activation that is characteristic of performing in a typical female way, during phases of the menstrual cycle characterised by low estrogen. Future studies should take this finding into consideration when conducting neuroimaging studies of sex differences in brain activation during performance on cognitive tasks.

Applying imaging techniques such as fMRI using a sex dimorphic cognitive battery in patients with schizophrenia may produce shifts in the neural substrates known to be activated by men and women during these tasks. These may underlie large differences between the controls and patients and could possibly contribute to differential disease expression between and within-sex.

Neurohormonal mechanisms

Much of our knowledge of the influence of sex hormones to cognition has come from (1) individual differences in endogenous levels of hormones, (2) normal fluctuations in hormone levels within one or the other sex (e.g. across the menstrual cycle in women, or from one season to another in men) and (3) exogenous hormone administration in men and women.

In general, studies of endogenous levels of gonadal hormones and cognition in both younger and older men and women report inconsistent findings. As discussed earlier, one of the major difficulties in interpreting findings from these studies is related to the different methods and procedures used. Studies in younger men and women have restricted the cognitive tests to spatial and verbal abilities, whereas studies in the older population have examined a wider range of cognitive abilities such as dart throwing (Janowsky et al., 1998) in men and women. Furthermore, a majority of studies examining the relationship of gonadal hormones to cognitive performance appear to be correlational and do not implicate causality. Study 1 looked at the relationship between a wide range of sexually dimorphic cognitive abilities (a range of spatial and both phonological and category fluency) and a wide range of hormones (gonadal and gonadotropins).

With regard to the relationship of gonadal hormones to brain activation during performance on cognitive tasks, there has been no study that has looked at sex differences in basal/endogenous levels of hormones on brain functioning in men and women. Study 3 is the first to look at this relationship using tasks that have previously been reported to show sex differences.

Menstrual cycle studies have provided evidence for activational effects of gonadal hormones on cognitive performance in young women. Some studies have found phase related differences in cognitive performance (verbal and spatial ability) in women (Hausmann et al., 2000; Hampson and Kimura, 1988; Hampson, 1990a; Philips and

Silverman, 1997) and others have not (Gordon et al., 1986; Gordon and Lee, 1993; Pomerleau et al., 1994; Epting and Overman 1998) (see chapter 1). Again, it is difficult to form definite conclusions about hormone-cognition relationships during the menstrual cycle because of the differences in methodology across studies. Another problem with these studies is the absence of accurate hormonal measurements in order to verify cycle phase (and to correlate hormone levels with cognitive performance). Some studies rely on self-reports. Epting and Overman (1998) reported that only 11 of 62 studies on cognition and menstrual cycle effects conducted hormone measurements. Furthermore, these studies cannot differentiate between the effects of estrogen compared to progesterone, although researchers have assumed that estrogen is the responsible hormone (Hausmann and Gunturkun, 2000). The current investigation obtained hormone measures (estrogen, progesterone, LH, FSH) in order to verify cycle menstrual cycle phase and examined the relationship of each gonadal hormone to cognitive functioning in men and women.

Studies of exogenous hormone treatment shed more light on the relationship of gonadal hormones to cognitive performance, although findings from these studies also demonstrate inconsistent findings (see chapter 1). For example, studies of testosterone administered to men in either the low physiological (e.g. to hypogonadal men) or in the supraphysiological ranges (e.g. in male contraceptive trials) have also produced inconsistent findings (Sih et al., 1997; Alexander et al., 1998; O'Connor et al., 2001).

Similarly, studies investigating the effects of estrogen replacement therapy in post-menopausal women have also produced inconsistent findings, with some reporting a beneficial effect of estrogen on cognitive performance (verbal memory, delayed verbal recall, working memory, frontal lobe mediated tasks; See Chapter 1). However, these positive findings are not limited to tasks that show sex differences, and other studies do not report any beneficial effects of estrogen replacement (e.g. Barret-Conner and Kritz-Silverstein, 1993).

Hormones that are administered in association with gender reassignment, is another area of hormone-cognition relationships that produces inconsistent findings. Some studies show estrogen treatment to impair spatial ability and improve verbal ability in male to female transsexuals, and the converse is reported for testosterone treatment in female to male transsexuals. (VanGoozen et al., 1995). However, this is not always reported (Miles et al., 1998; Slabbekoorn et al., 1999).

Generally, the absence of consistent findings from exogenous hormone treatment studies can be related to; (1) the different measures of hormones taken, (2) different hormone assays used to determine hormone levels, (3) the duration of hormones used may vary across studies, (4) different tests are used to measure domains of cognitive functioning across studies (5) studies differ in the dosages of hormones administered, some administering estrogen, others estrogen and progesterone, (6) studies differ in the ages of participants and, (7) not all studies have not taken into account past history of hormone treatment.

In order to fully understand the relationship of gonadal hormones to cognitive functioning, it is necessary to understand the physiological mechanisms through which hormones act. The hypothalamus, a major relay station, secretes specific releasing hormones, leading the pituitary to produce tropic (stimulating) hormones directly into the blood. The tropic hormones (e.g. gonadotropins) reach the receptors of their respective target glands (the ovaries or the testis), and the end organ is stimulated to secrete a particular hormone. The ovaries produce a group of hormones called estrogens and the testis produce a group of hormones called androgens, the most powerful of which is testosterone. It is important to note that although estrogen is generally associated with women and androgens with men, the sex difference rests in the relative amounts of the two hormones, so that both sexes produce some of each hormone, and both sexes convert some of each hormone to the other. This conversion process significantly complicates hypotheses concerning the impact of high levels of testosterone and estrogen on behaviour. A way in which the production of these hormones is regulated is via a feedback loop. Among the targets reached by the secreted hormones from the end

hormone is the hypothalamic-pituitary axis itself. When that axis detects too little or too much of a particular hormone, it causes an increase or a decrease in the appropriate tropic hormone, with a resultant increase or decrease in testosterone or estrogen (Griffin and Ojeda, 1996).

Animal studies have demonstrated ways in which gonadal hormones exert their influence on cognition, mood and mental state. Recent experimental studies have found that the effects of gonadal hormones may be mediated by serotonin, an important neurotransmitter, dysfunction of which has been implicated in schizophrenia (Fink and Bicknell, 2000). In the female rat estrogen has shown to increase the expression of genes for the 5HT2A receptor and the serotonin transporter in regions of the forebrain that in humans are related to cognition, memory and mental state. Similarly, in the male rat estrogen and testosterone (through conversion to estrogen by aromatase) also increase the density of 5HT2A receptors in the forebrain. One study in humans showed a decreased prolactin response to d-fenfluramine (a 5-HT releasing and re-uptake inhibiting agent) in postmenopausal estrogen naïve women compared to postmenopausal women on estrogen and young women (van Amelsvoort et al., 2001). These finding lends support to the theory that estrogen modulating age related changes in 5-HT tone may relate to cognitive changes and the decrease in vulnerability to disorders such as depression and schizophrenia in postmenopausal women

Another way in which gonadal hormones can relate to cognitive functioning and the onset of schizophrenia is related to the neuroendocrine changes in the basal forebrain in the initiation of and throughout the reproductive period. This period is associated with the developmental of regular pulsatile release in the brain and bloodstream of gonadotropic releasing hormones from the hypothalamus, LH and FSH from the pituitary and gonadal hormones from the ovaries and testes. As well as being concentrated in the hypothalamus, brain receptors for gonadotropic and gonadal hormones are concentrated in specific subcortical forebrain nuclei of the limbic system that project to the thalamus, and to cortical and subcortical regions that represent perception, cognition and behaviour. To avoid hyperexitability, the surge of the excitatory hormones (estrogen and

testosterone) must be counterbalanced by appropriate inhibitory factors. Greater focal inhibition may be induced by increased release of or increased receptors for one or more inhibitory transmitters e.g. dopamine, serotonin, and γ-aminobutyric acid in the anterior basal forebrain. Changes in these processes can relate to changes in mental state, cognition and behaviour in schizophrenia.

A possible reason for the findings from the current investigation in relation to cognitive functioning and symptomatology could be related to the interaction between neurotransmitters and gonadal hormones, which in conjunction may differentially affect cognitive performance in both healthy men and women and patients with schizophrenia.

Another brain region, the hippocampus, has been associated as a possible brain region for the action of estrogen and androgen on cognitive, particularly declarative memory and spatial performance. Studies of the role of estrogen on the hippocampus are indirect and come from the effects of hormone replacement therapy on hippocampal-dependent cognitive processes such as explicit memory or free recall. The hippocampus contains both testosterone and estrogen receptors (Roof and Haʏens, 1992;Luine, 1994). Testosterone may have direct effects on the hippocampus through the androgen receptor, as well as indirect effects from aromatization to estradiol interacting with estradiol receptors (Naftolin et al., 1975).

Findings from the current investigation are unprecedented and could be related to an interaction of gonadal hormones with hippocampal functioning. For example, the relationship of T to spatial memory in women with schizophrenia may have been related to T actions within the hippocampus. This conclusion is tentative but offers a possible explanation for the pattern of findings observed.

Studies examining the role of gonadal hormones in brain activation during performance on mental rotation and language tasks also fail to find any relationships between hormones and cognition (Dietrich et al., 2001; Veltman et al., 2000). Though Dietrich and colleagues found an increase in hemodynamic response in women during the high

estrogen phase of the menstrual cycle during a word completion and mental rotation performance and Veltman et al. (2000) during both phases, they found extensive activation in left superior parietal, motor and prefrontal cortices and bilateral cerebellar, striatal and extrastriatal cortices during performance of a rhyme decision task. None of these studies took measures of hormone levels in order to (a) relate levels of hormones to cognitive performance and (b) verify menstrual cycle phase.

Imaging studies that manipulate gonadal hormone levels provide a better picture of the effect of hormones on cognition in the brain. An fMRI study by Shaywitz et al. (1999) in postmenopausal women, scanned twice (on estrogen, then placebo), whilst performing verbal and non- verbal working memory tasks showed that estrogen treatment increased activation in the IPL during storage of verbal material, and deactivation of the IPL during storage of non-verbal material. Increased estrogen related activation was also observed in the right superior frontal gyrus during retrieval tasks, coupled with greater left hemisphere activation during encoding. Also, findings from a PET study showed that in the absence of ovarian hormones (induced by a gonadotropins-releasing hormone agonist), diminished activation of the areas reported to be activated by the WCST was found (no rCBF in PFC), with no change in behavioural performance (Berman et al., 1997). This was normalised when estrogen or progesterone were added to the agonist (Lupron) in young women. Similarly, another PET study in older women on and off estrogen, replacement therapy showed that both groups showed differences in rCBF in frontal regions, parahippocampal gyrus, left hypothalamus, right precuneus during a verbal memory task (Resnick et al., 1998) and that longitudinal rCBF changes (over 2 years) in estrogen compared to non-treated women was more pronounced in the hippocampus, parahippocampal gyrus, and temporal lobe during a verbal and figural recognition task (Maki and Resnick, 2000).

Whether and to what extent hormones relate to cognitive performance is unclear, and may relate to a complex façade of events involving hormones and their interaction with different neurotransmitters and neural pathways.

The existence of sex differences is not only attributed to levels of, or fluctuations (activational) in levels of gonadal hormones. At one end of the spectrum, some argue that all behavioural sex differences are the product of cultural socialisation (e.g. Bem, 1983, 1993). At the other end, there are those who argue that these differences are largely explained by the different biological endowments of men and women, albeit in interaction with individual experiences (Silverman and Philips, 1993). An interaction of both biological and psychosocial factors can influence the cognitive development of individuals. Some authorities have suggested that environmental factors such as socialisation for sex-differentiated play, leisure activities, and educational experiences can contribute to sex differences for example in spatial skills (Sharps et al., 1994, Etaugh, 1983). Correlational data have shown significant links between selected kinds of experience and spatial skills (e.g. Newcombe et al., 1983). However, the causal explanation of these relationships is uncertain. Some of the questions that arise from this thesis are whether sex related differences in cognitive ability could be attributed to the biology of the female and male? Or are biological factors, such as gonadal hormones that can make you more male or female unrelated, to the types of cognitive abilities that we develop?

Overall, the findings from the current investigation appear to be a result of the partnership between complex biological (hormone-brain relationships) and psychosocial (e.g. environment, occupational, leisure) factors working together to form differential relationships of gonadal hormone–cognition relationships in individuals.

Improvements to the investigation and future research.

The present studies may have benefited from some improvements that need to be considered in future investigations. In study 1 and 2, measures of gonadal hormones were obtained at a single time point. Although the aim of the thesis was to examine basal/endogenous levels of hormones in men and women, taking measures of some hormones such as testosterone in the morning and afternoon, and cortisol at several time points (e.g. 9 a.m., 11.a.m, 1.p.m), would give a better indication of the intra-individual

variability in the hormone levels in both healthy men and women and patients with schizophrenia. Testosterone levels have been reported to be at the highest in the afternoon compared with morning levels (Dabbs, 1993). Future studies should take measures of hormones other than estrogen and testosterone when examining relationships between hormones and cognition, as the present thesis found associations between a stress hormone and gonadotropins and cognitive performance. Also, taking measures of gonadal hormone levels before and after scanning is important in understanding the relationship between hormones and task performance in the scanner.

Because of the small sample size in study 2, menstrual phase related differences were difficult to examine. The abnormally high levels of gonadotropins in some female subjects made it difficult to ascertain what phase of the menstrual cycle they were in, or if they were postmenopausal. Together with their hormonal profile it would be important to collect information from the clinicians, as well as self-reports on their menstrual history, their last period, duration of period and age at onset of puberty.

A better picture of the relationship of hormones to cognitive functioning may be achieved by testing medication naïve subjects; this would provide insight into how hormones affect cognition without the confounding effects of different types of medication. As discussed above, estrogen as well as antipsychotic medication can affect neurotransmitters in the brain.

A range of potentially confounding factors such as socio-demographic variables, years in education, level of education, ethnic grouping, parental socio-economic status, sex-typed occupational choice, perceived levels of stress during neuropsychological testing and degree of right-handedness may have impinged upon the results and were not matched between the groups, and therefore may explain the absence of any associations of gonadal hormones with cognitive performance findings. Thus, if differences did exist between the sexes on these variables, it may suggest the possibility that "lifestyle" differences between the groups are responsible for the findings.

The profile of mood questionnaire (Lorr and McNair, 1988) should have been included in these studies to examine whether mood contributed to cognitive performance in men and women. In particular, mood may have been disrupted in women tested during the low estrogen phase of the menstrual cycle.

Participants in the studies should have been asked about their age of pubertal onset. This measure can also provide indices of whether early maturation relates to better or worse cognitive performance in men and women, and may also explain whether hormone-cognition relationships would be found in these individuals.

With regard to the fMRI studies, event related designs (examining brain activation in relation to particular time points (events) during task performance) may give a better picture as to what areas are activated during certain trials (i.e. as the angular disparity increases for the mental rotation task), and this could be correlated with hormone levels to establish whether any relationship exists between these trials and estrogen and testosterone levels in men and women.

Task difficulty should have been factored in the mental rotation and verbal fluency tasks. Men and women may have differed in brain activation in the harder conditions of the rotation conditions for the mental rotation task (i.e. all the angles rotated from 80° to 180°, on the z axis).

In future studies men and women that do not differ in behavioural performance, as well as those that do, should be included in fMRI studies of mental rotation and verbal fluency, so that brain activation between thhe sexes can be compared in th epresence and absence of performance differences. Other neuroimaging techniques can also help to understand how hormones exert their influence in the brain in relation to cognitive performance. PET studies can help to determine hormonal and neurotransmitter receptor binding, for example, before and after hormone administration (Akira et al., 2003).

The studies in the present thesis add to a growing body of robust empirical work that is critical of the purported relationship between basal/endogenous levels of gonadal hormones, cognitive and brain functioning (a select sample includes Miles et al., 1998; Dietrich et al., 2001, Gordon et al., 1986). They suggest that, although there may be some association between these variables, the patterns of relationships are often specific if not weak at best. They point primarily to the importance of methodological rigour in future work. The relationships between gonadal hormones and neurocognitive performance in healthy adult males and females, and those with chronic schizophrenia, are much less clear than previously thought.

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