1-1-2012

Effects of sex, free testosterone, and androgen receptor cag repeat number on spatial cognition and virtual navigation performance

Nicole Therese Nowak
Wayne State University,

EFFECTS OF SEX, FREE TESTOSTERONE, AND ANDROGEN RECEPTOR CAG REPEAT NUMBER ON SPATIAL COGNITION AND VIRTUAL NAVIGATION PERFORMANCE

by

NICOLE T. NOWAK

DISSERTATION

Submitted to the Graduate School

of Wayne State University,

Detroit, Michigan

in partial fulfillment of the requirements

for the degree of

DOCTOR OF PHILOSOPHY

2012

MAJOR: PSYCHOLOGY (Behavioral and Cognitive Neuroscience)

Approved by:

_____

Advisor Date

_____

_____

_____

_____

ACKNOWLEDGEMENTS

I would like to thank my dissertation advisor, Dr. Scott Moffat, for his financial support and patience over the years; committee member Dr. Michael Diamond for his donation of laboratory space; committee members Dr. John Hannigan, and Dr. Michelle Tomaszycki for their expertise and time; and Dr. Glenn Weisfeld for his membership on this committee and ongoing support. I am grateful to Victoria Good, who spent many unpaid hours scoring questionnaires and entering data; Roy and Karen Collins, and Mindy Perez for passing along their expertise in laboratory techniques; Evette Garcia for meeting the scheduling demands of this study; Alia Allen, for her support, and help wading through the paperwork and deadlines; the Wayne State Applied Genomics Technology Center for quantification of the androgen receptor data; Quest Diagnostics for providing hormone data; and my participants for their time, effort, and blood. I am thankful for the support, kindness, humor and love of my husband and close family members. I am fortunate to have made a few good friends during graduate school, and am proud to know we will always share a unique bond. Finally, I acknowledge my friends from Minnesota who have remained close throughout the years of biannual visits.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1

INTRODUCTION

The fact that men and women differ is a stimulating topic among scientists from diverse disciplines. Several theories can be applied to explaining how and why the sexes differ, and most researchers agree that several sources of behavioral variability contribute to these differences (e.g., evolution, development, genetics, hormones, experience). This dissertation integrates literature from the behavioral, neuroscience, and behavioral neuroendocrinology perspectives; and hypothesizes that interactions between testosterone (T) and an additional measure of androgenicity (androgen receptor CAG repeat; CAGr) are relevant to the explanation of spatial performance.

The purpose of this dissertation is twofold: (1) review the effects of sex and androgens on spatial cognition, and (2) investigate the effects of sex, T, and CAGr on spatial cognition, virtual navigation performance, and navigation-related experience. The primary focus is on human research; however, studies that used nonhuman animals such as rodents are also represented. The literature review begins by reviewing the male advantage in spatial performance, particularly three-dimensional (3D) mental rotation and navigation, and discusses neuroimaging studies of sex differences in brain activity while performing these tasks. The final sections of the review discuss prenatal and adulthood effects of androgens on spatial performance.

1.1 Sex Differences in Performance on Psychometric Measures of Spatial Cognition

Men and women differ negligibly, or not at all, on standardized tests of intelligence (e.g., Kaufman, 1990; Koscik, O'Leary, Moser, Andreasen, & Nopoulos, 2009; Maccoby & Jacklin, 1974; Matazarro, 1972); however, women often excel on

language related tasks (for review see Ullman, Miranda, & Travers, 2008) and men excel on tasks of spatial performance (for reviews and meta-analyses see Coluccia & Louse, 2004; Hyde, 1981; Linn & Petersen, 1985; Maccoby & Jacklin, 1974; and Voyer, Voyer, & Bryden, 1995), with the exception of a female advantage in object location memory (Eals & Silverman,1994; McBurney, Gaulin, Devineni, & Adams, 1997). Several reviews and meta-analyses describe and quantify the male advantage in visuospatial performance (Hyde, 1981; Linn & Petersen, 1985; Maccoby & Jacklin, 1974; and Voyer et al., 1995). Linn and Petersen (1985) reported the effect of sex on three categories of spatial ability in their meta-analysis. Spatial perception (e.g., Rod and Frame Test) was defined as the ability to "determine spatial relationships with respect to the orientation of their own bodies, in spite of distracting information", and the effect size of the sex difference was moderate. The second category, spatial visualization (e.g., Block Design, Minnesota Paper Form Board, Paper Folding), was defined as the ability to perform "complicated, multistep manipulations of spatially presented information", and the average effect size of the sex difference was small. The third category was mental rotation (e.g., Cards Rotation Test, Mental Rotations Test) and was defined as the ability to "rotate a two or three dimensional figure rapidly and accurately". The effect size for the sex difference in overall mental rotation ability was 0.73, and 0.94 for the Vandenberg and Kuse (1978) 3D Mental Rotations Test (MRT). Another meta-analysis on the topic of sex differences in spatial cognition reported that mental rotation performance elicited effect sizes favoring males that ranged from one half to one standard deviation (Voyer et al., 1995).

1.2 Sex Differences in Spatial Navigation

Spatial navigation, or wayfinding, is another domain of human spatial cognition where a male advantage has been observed. Navigation and wayfinding, used here interchangeably, may be defined as knowing where we are in space and navigating to specific destinations in the environment both mentally and behaviorally (Passini, 1984). Coluccia and Louse (2004) published a review of sex differences in wayfinding abilities (e.g., orienteering, route reversal, pointing, distance estimation, landmark recall, wayfinding based on Euclidean or landmark strategy, computerized maze learning, route learning based on video recordings) and reported a significant male advantage in at least 53% of the studies with 12% revealing a female advantage. The findings reveal an overall male advantage, but suggest this may depend on the navigation task.

While the review by Coluccia and Louse (2004) is descriptive and informative, an adequate number of studies exist to perform a meta-analysis on the magnitude of the male advantage in real-world and computerized navigation tasks; however, one has yet to be published. For example, a moderate effect size (d = .37) was reported for a map-based route learning task (Galea & Kimura, 1993), while large effect sizes favoring males were found for an orienteering drill (d = .80) (Malinowski & Gillespie, 2001) and a computerized maze learning task (d = 1.40 to 1.59) (Moffat, Hampson & Hatzipantelis, 1998).

In the 1990s researchers developed computerized counterparts of traditional rodent learning and memory tasks such as the Morris water maze (Morris, 1984) and hallway/corridor mazes for use in human behavioral and neuroimaging research. Although variety exists in the versions of the vMWT used for testing (e.g., cues available to locate the hidden platform may differ in type or number), the basic procedure

parallels that of Morris's original water maze. Rather than being placed in a real pool of water, humans view the water maze on a desktop computer screen and locate the hidden platform by maneuvering through the pool with a joystick. Dependent variables of the original water maze and the vMWT include: time and distance to locate hidden platform across learning trials, time and distance spent in the platform quadrant during the probe trial, platform area crossings during the probe trial, and time and distance taken to locate a visible platform.

Sex differences in learning and probe trial performance exist in water maze performance for rodents and humans. The swim/visible platform trial is used as a visuomotor control in rodents and humans and the lack of sex difference on these trials is evidence that the male advantage is not due to swimming skill or exploratory behavior in rodents, or joystick use in humans. A meta-analysis of water maze performance in rodents revealed a moderate effect size favoring males (Jonasson, 2005). A sex difference favoring men in vMWT performance has also been reported (Astur, Ortiz, & Sutherland, 1998; Astur, Tropp, Sava, Constable, & Markus, 2004; Burkitt, Widman, Saucier, 2007; Driscoll, Hamilton, Yeo, Brooks, & Sutherland, 2005; Mueller, Jackson, & Skelton, 2008; Nowak & Moffat, 2011; Rahman & Koerting, 2008; Sandstrom, Kaufman, & Huettel, 1998) with several effect sizes as large or larger than one standard deviation (e.g., Astur et al., 1998; Mueller et al., 2008; Nowak & Moffat, 2011).

The second traditional rodent task with a virtual counterpart is the corridor/hallway maze. Similar to maze tasks used to study rodent learning and memory, these virtual corridor mazes begin with a start location, include interconnecting corridors with multiple decision points and opportunities for memory errors and

backtracking, sometimes include landmarks, and are complete when the participant enters the goal area. The dependent variables, such as number of errors, time taken to navigate from start to goal, and number of trials to criterion are also consistent between the rodent and human tasks.

A moderate male advantage exists in maze performance for rodents (e.g., for meta-analysis and review, see Jonasson, 2005). Effect sizes favoring men in fewer numbers of maze navigation errors and quicker time to completion are moderate to large (e.g., Grön, Wunderlich, Spitzer, Tomczak, & Riepe, 2000; Moffat et al., 1998; Moffat, Zonderman, & Resnick, 2001).

1.3 Sex Differences in Brain Activation While Performing Spatial Tasks

Given the reliable sex difference at the behavioral level of analysis, it is logical to predict that men and women are recruiting different brain regions to solve 3D mental rotation and navigation tasks. The data summarized in the next two sections are based on functional magnetic resonance imaging (fMRI) studies. Functional MRI results are specifically based on the blood-oxygenation-level-dependent (BOLD) response, which is assumed to correlate with neuronal activity evoked by cognitive processes (e.g., Kwong et al., 1992; Ogawa, Lee, Nayak, & Glynn, 1990). The term “brain activity/activation” is often used interchangeably with “BOLD response” in the cognitive neuroscience literature, and will be here as well.

1.3.1 Sex Differences in Brain Activation While Performing Mental Rotation Tasks

The data summarized in Table 1 suggest that men and women both rely on parietal lobe function during mental rotation of 3D objects, but that sex differences also exist in recruitment of the parietal lobes. Evidence from animal (e.g., Morton & Morris,

1995), clinical lesion (e.g., Tomasino & Rumiati, 2004), and human studies (e.g., Michel, Kaufman, & Williamson, 1994) indicates that the parietal lobes are involved in spatial relations, allocation of visual attention, maintaining multiple spatial representations, encoding visual stimuli, visual search, and object recognition (e.g., Cohen et al., 1996; Colby, Duhamel & Goldberg, 1995; Corballis, 1997; Richter et al., 2000; Vingerhoets, de Lange, Vandemaele, Deblaere, & Achtem, 2002).

Regarding the sex differences in brain activation, there was some consistency across the five studies (Table 1). The most consistent sex difference found among the studies that compared brain activation of men and women during mental rotation was the greater activation of the right inferior frontal gyrus in women. This result has been commonly interpreted as women relying on a verbal or piecemeal strategy, although assessment of strategy was not reported in any of these experiments. Despite this gap between measurement and interpretation, support exists for the role of the right inferior frontal gyrus in verbal task performance of women (e.g., Jaeger et al., 1998; Kansaku, Yamaura, & Kitazawa, 2000) as well as visual spatial working memory (Jordan et al., 2002; Leung, Oh, Ferri, & Yi, 2007; Zago et al., 2008). It is possible, for example, that while women are performing 3D mental rotation, they are regularly giving themselves verbal instructions while holding mental images and transformations of these images in working memory, while men are relying more on the visual and spatial features of the mental rotation task.

The same degree of consistency does not exist when looking for a pattern of greater activation in men compared to women. Regions of the parietal lobes were activated during mental rotation more in men than women in three of the five studies,

and again this has been interpreted in terms of strategy, namely that men utilize a gestalt rotation process. Recently, the sex differences in parietal lobe anatomy, particularly the increased gray matter in women and larger surface area in men, have been related to MRT performance (Koscik et al., 2009). Within the male sample only, men with greater parietal lobe surface area had better MRT scores than those with less surface area. Unique to the female sample, having more parietal gray matter than white was associated with poorer MRT performance (Koscik et al., 2009). Given the primary role of the parietal lobes in mental rotation, sex differences in parietal lobe anatomy (e.g., Koscik et al., 2009; Nopoulos, Flaum, O'Leary, & Andreasen, 2000), and recent evidence linking this anatomy with MRT performance, it is reasonable to speculate that parietal lobe structure and function at least partially account for the sex difference in MRT performance.

1.3.2 Sex Differences in Brain Activation While Performing Navigation Tasks

There is a gap in our knowledge between sex differences at the behavioral level and those at the functional neuroanatomical level. Conclusions from the behavioral literature are consistent; there is a moderate to large male advantage on real world and virtual navigation tasks. The two fMRI studies that compared the BOLD response of men and women while performing virtual navigation tasks produced somewhat contradictory results (Grön et al., 2000; Ohnishi, Matsuda, Hirakata, & Ugawa, 2006). If there is common ground between the studies, it is that the left hippocampus and parahippocampal gyri are associated with good navigation performance, whereas the right inferior and superior parietal lobes are associated with relatively poorer performance. The hippocampus has a well-established role in successful navigation

across species including food-caching birds (e.g., Petersen & Sherry, 1996; Vaccarino, Buckenham, & Herz, 1989), homing pigeons (e.g., Bingham, Ioale, Casini, & Bagnoli; Rehkamper, Haase, & Frahm, 1988), rodents (e.g., D'Hooge & De Deyn, 2001; O'Keefe & Dostrovsky, 1971; O'Keefe & Nadel, 1978; O'Keefe & Speakman, 1987; Poucet & Benhamou, 1997; Redish, 1999; Sherry, Jacobs, & Gaulin, 1992), and humans (e.g., Astur, Taylor, Mamelak, Philpott, & Sutherland, 2002; Barrash, 1998; Barrash, Damasio, Adolphs, & Tranel, 2000; Ekstrom et al., 2003; Kessels, de Haan, Kappelle, & Postma, 2001; Maguire, Frackowiak, & Frith, 1996, 1997; Maguire et al., 1998). The role of the parahippocampal gyri in navigation has also been established; for example, in the use of landmarks (e.g., Maguire et al. 1998; Janzen & van Turennout, 2004) and learning and memory of the geometry of an environment (e.g., Epstein & Kanwisher, 1998). Collectively, these data lead one to hypothesize that the hippocampus and parahippocampal region will be associated with relatively good navigation performance in future fMRI studies.

Previous sections have discussed sex differences in performance of traditional tests of spatial cognition and navigation at the behavioral and functional neuroanatomical levels. Another approach to explaining the sex differences in spatial cognition comes from behavioral endocrinology. These final sections of the review focus on the literature that has examined neuroendocrine explanations for the variability in spatial performance, primarily the influence of T on performance.

1.4 Androgens

Prior to summarizing their effects on spatial cognition, a brief overview of androgens will be provided. Androgens comprise one class of sex steroid hormones

(e.g., Brown, 1994). Sex steroid hormones bind to intracellular receptors to promote biological action, namely the regulation of gene transcription (e.g., Brown, 1994; Mendelson, 2004). Androgens are synthesized from cholesterol via a number of pathways and enzymatic steps (e.g., Griffin, 2004). The testes are the primary source of androgens in males (e.g., Brown, 1994), while the adrenal cortices and ovaries are the primary sources of androgens in females (e.g., Rosen & Cedars, 2004). Androgens that are not bound to the proteins sex hormone binding globulin (SHBG) or albumin, (approximately two percent) are "bioavailable" (i.e., available to diffuse across cell membranes and bind with nuclear androgen receptors) (e.g., Griffin, 2004). Androgens dissociate more readily from albumin than they do SHBG (Pardridge, 1986), and androgens bound to albumin readily travel to the brain (Griffin, 2004).

After the gonads or adrenal glands produce T, it has the potential to travel through the bloodstream to the brain, where it can affect cognition. There are two mechanisms by which T affects androgen receptors (AR) in the brain: (1) bind to ARs directly, (2) bind to ARs after conversion to dihydrotestosterone (DHT) via the enzyme 5α-reductase (e.g., Fernández-Guasti, Kruijver, Fodor, & Swaab, 2000).

Androgen receptors bind all androgens but have the greatest affinity for DHT and T (Wilson & French, 1976). ARs are widespread throughout the body, including the central nervous system. Receptors are present in the brains of rhesus monkeys, including the hypothalamus, anterior pituitary, amygdala, parietal cortex, and hippocampus (Abdelgadir, Roselli, Choate, & Resko, 1999; Choate, Slayden, & Resko, 1998). ARs are widespread in the rodent hippocampus, septum, amygdala (e.g., Kerr, Allore, Beck, & Honda, 1995; Roselli, Handa, & Resko, 1989; Sar & Stumpf, 1975),

hypothalamus (e.g., Madeira, Ferreira-Silva, Paula-Barbosa, 2001), and parietal cortex (Roselli et al., 1989). Sex differences in AR expression are most notable in the hypothalamus (e.g., Roseli, 1991), and also occur in the hippocampus (e.g., Xiao & Jordan, 2002). Much less is known about the distribution of ARs in the human brain; however, the sex difference in hypothalamic AR has been replicated in humans (Fernández-Guasti, Kruijver, Fodor, & Swaab, 2000). Similar to rodents and primates, ARs are present in the human temporal cortex (Puy et al., 1995) including the hippocampus (Beyenburg et al., 2000; Tohgi, Utsugisawa, Yamagata, & Yoshimura, 1995).

1.5 Organizational and Activational Effects of Androgens on Spatial Performance

Organizational effects are commonly defined as permanent hormonal effects on neural structures and connections that take place during a critical prenatal and/or perinatal period (Phoenix et al., 1959). Organizational effects of androgens include influence on cell number, size, and patterns of connection; neurotransmission; stability of synaptic contacts (McEwen, 1981); neuroplasticity (see Leranth, MacLusky, & Hajszan, 2008 for review of sex differences in neuroplasticity); cell death (e.g., Forger, 2009); sensitivity to circulating androgens in adulthood, and adulthood androgen concentrations (e.g., Jamison, Meier, & Campbell, 1993; Meikle, Stringham, Bishop, & West, 1988). The critical period for organizational effects of androgens on human spatial cognition is unknown; however, gestational week 16 may mark the peak of this period given the maximal sex difference in androgen production at this time (Smail et al., 1981).

Although the distinction between organizational and later life hormonal effects is somewhat arbitrary (Arnold & Breedlove, 1985) because these events are not orthogonal, it is routine to heuristically characterize them as *organizational* or *activational* (Phoenix et al., 1959). *Activational effects* of androgens on the brain and behavior are commonly thought of as reversible effects upon the neural structures and connections established during early development (e.g., Arnold & Breedlove, 1985; Eckel et al., 2008). Activational effects are more transient short-term effects that take place in adulthood.

1.6 Organizational Effects of Androgens on Spatial Cognition

The significance of organizational effects is that the pre/perinatal hormonal status of a developing animal affects brain structure and function and subsequent spatial performance. Animal models provide the opportunity to manipulate pre/perinatal androgens and study the effects on brain function as well as spatial behavior, whereas human models rely strongly on clinical conditions such as congenital adrenal hyperplasia (CAH).

1.6.1 Perinatal Androgen Manipulation

Evidence for the notion that perinatal androgens affect adult spatial cognition is apparent in several studies showing an enhancing effect of T administration on adult spatial performance in normal female rodents and a detrimental effect following removal of the endogenous T source in males. Thus, neonatal castration impairs adulthood spatial performance in male rats (e.g., Dawson, Cheung, & Lau, 1975; Isgor & Sengelaub, 2003; Joseph, Hess, & Birecree, 1978; Williams, Barnett, & Meck, 1990). and neonatal T administration enhances adulthood spatial performance in females (e.g.,

Dawson et al., 1975; Isgor & Sengelaub, 1998, 2003; Joseph et al., 1978; Roof, 1993; Roof & Havens, 1992; Stewart, Skvarenina, & Pottier, 1975). At least one study has shown that gonadally-intact males treated with T during the first postnatal week actually perform worse than gonadally-intact control males in adulthood (Roof & Havens, 1992), providing support for the notion that either too little or too much T can be detrimental to spatial cognition in males.

1.6.2 Intrauterine Position

Another approach to the study of organizational hormonal effects on spatial abilities is the use of the intrauterine position paradigm . This approach is partly based on the observation that female rats adjacent to two male rats *in utero* were found to have higher serum and amniotic fluid T concentrations than females adjacent to other females (vom Saal & Bronson, 1978; vom Saal et al., 1990). This raises the question of whether females exposed to higher levels of androgens *in utero*, by virtue of fetal androgens diffusing across placental barriers (e.g., Ryan & Vandenbergh, 2002), may be more masculinized than females surrounded by other females. Females surrounded by males were found to be physiologically (e.g., increased sensitivity to T), physically (e.g., more male typical anogenital distance) and behaviorally (e.g., more aggressive) more masculine than females surrounded by females (reviewed in Ryan & Vandenbergh, 2002). This endocrine and behavioral masculinization also extended to spatial behaviors as females surrounded by males were found to perform better in a radial arm maze than females surrounded by other females *in utero* (e.g., Clemens, Gladue, & Coniglio, 1978).

Cole-Harding, Morstad, & Wilson (1988) questioned whether human females with male co-twins would perform better on a mental rotation task during adulthood than females with female co-twins. The females with opposite sex co-twins performed just as well as their male twins on the MRT. Although this finding may be interpreted as evidence that an androgen rich prenatal environment can masculinize the mental rotation ability in females, it may also be the case that girls who have twin brothers have higher MRT scores for some experiential reasons such as postnatal play experiences with a male twin.

1.6.3 Congenital Adrenal Hyperplasia (CAH)

Manipulation of prenatal hormones in humans for the sake of research is unethical, so some researchers have taken the opportunity to study the organizational effects of androgens on spatial cognition through clinical disorders such as CAH. Approximately 1 in 16,000 live born infants have experienced abnormally high levels of adrenal androgens due to genetic defects in the synthesis of corticosteroids in the adrenal cortex (Carlson, Obeid, Kanellopoulou, Wilson, & New, 1999; New, Dupont, Grumbach, & Levine, 1983). As a result of the dysfunctional enzyme 21-hydroxylase, androgen levels are increased due to an abundance of androgen precursors, and chromosomal females are partially masculinized (e.g., some degree of genital virilization). For example, it is possible for a female fetus with CAH to have a male-typical androgen level (e.g., Pang, Levine, Chow, Faiman, & New, 1979). The overproduction of androgens is hypothesized to exert relatively permanent organizational effects on the brain, which in turn may affect behavior, anatomy and physiology that is sensitive to prenatal androgen levels.

Several studies have addressed the effects of abnormally elevated androgen levels on different cognitive performances, but only a few were designed specifically to evaluate spatial abilities (e.g., Resnick, Berenbaum, Gottesman, & Bouchard, Jr., 1986; Hampson, Rovet, & Altmann, 1998; Hines, Fane, Pasterski, Matthews, Conway, & Brook, 2003). Overall, females with CAH outperform unaffected control females in the spatial domain and this effect is moderate (*d* = .30 to .60), while the opposite effect was found for males with CAH in that they performed worse than unaffected control males on spatial tasks (*d* = -.58 to -.60) (for meta-analysis see Puts, McDaniel, Jordan, & Breedlove, 2008). This differential consequence of increased prenatal androgens on the spatial performance of males and females with CAH, coupled with data from unaffected genetic controls, is commensurate with the theory of an optimal level of T for spatial performance.

1.6.4 Polycystic Ovarian Syndrome (PCOS)

The cause of PCOS is not altogether clear, but some have suggested a strong heritable component and X – linked genetic transmission (e.g., Govind, Obhrai, & Clayton, 1961), while others have provided some evidence for abnormality in the regulation of the enzyme cytochrome P450c17 alpha, a rate limiting factor in the synthesis of androgens (Rosenfield, Barnes, Cara, & Lucky, 1990). PCOS affects up to 10 percent of women in their reproductive years, with the onset frequently being observed in the perimenarcheal phase of development (Stein & Leventhal, 1935; Torpy, Lynm, & Glass, 2007).

Given that a hallmark of PCOS is hyperandrogenism, it is surprising that few publications have addressed spatial performance in this group of women. If the free T

level that corresponds with optimal spatial performance lies between the high normal range for women and the low normal range for men, then women with PCOS would be expected to perform better than most women. Barnard, Balen, Ferriday, Piplady, and Dye (2007) found that women who had PCOS did not differ from control women on a mental rotation task, regardless of whether the PCOS women were taking anti-androgen medication. The PCOS women performed significantly worse on some measures that usually favor females over males. The primary shortcomings of this study were the Internet survey-based method used to collect data (e.g., self-reported diagnosis and treatment, online cognitive testing), and the lack of T measurement.

Schattmann and Sherwin (2007) tested PCOS and control women on four measures of visuospatial ability that often favor males and several other cognitive tasks that often favor females. The PCOS women performed significantly worse on some measures that usually favor females. Free androgen level did not correlate with any of the visuospatial tasks, nor were group differences found on the MRT.

In the second study by Schattmann and Sherwin (2007), they pharmacologically reduced T levels in a PCOS group and tested visuospatial cognition before and after three months of treatment with cyproterone acetate (anti-androgen plus estrogen). Free androgen levels did not significantly correlate with any of the visuospatial tasks at any time, nor was there a significant change in performance from pre- to post-treatment.

Taken together, the studies of women with PCOS do not support the idea that androgen levels above the normal range confer an advantage on spatial tasks such as mental rotation.

1.7 Activational Effects of Androgens on Spatial Cognition

In addition to early life effects of androgens on spatial cognition, there is evidence to support an activational role of androgens on adulthood spatial cognition in nonhuman and human animals. While organizing effects are thought to permanently affect brain structures and function during critical periods of pre/perinatal development, activating effects of androgens influence brain function transiently by affecting the androgen-androgen receptor binding process and subsequent transcription of androgen dependent genes (e.g., Mendelson, 2004), neuronal structure (Gould, Woolley, Frankfurt, & McEwen, 1990), and neurotransmitter synthesis (Arnold & Breedlove, 1985; McEwen, 1981).

1.7.1 Adulthood Castration and Effects of Flutamide – Nonhuman Animals

Adulthood castration (e.g., Hasegawa & Mochizuki, 2009; Spritzer, Gill, Weinberg, & Galea, 2008) and intrahippocampal injection of T to normal males (Harooni, Naghdi, Sepehri, & Rohani, 2008) have negative effects on the spatial performance of rodents. Detrimental effects of castration on spatial working memory performance, and restorative effects of T treatment after castration, have been reported by several researchers (Daniel, Winsauer, & Moerschbaecher, 2003; Gibbs, 2005; Kritzer, McLaughlin, Smirlis, & Robinson, 2001; Sandstrom, Kim, & Wasserman, 2006). For example, Sandstrom et al. (2006) found no effect of castration on traditional Morris water task learning and probe trials, but found that castrated males performed worse than controls on a modified spatial working memory version of the task. The results of this experiment were strengthened by the fact that T replacement in the castrated group restored performance to that of controls. In contrast, several studies have found no effect of male castration or androgen administration to females on spatial performance

in adulthood (e.g., Beatty, 1984; Dawson, Cheung, & Lau, 1975; Isgor & Sengelaub, 1998; Stewart, Skvarenina, & Pottier, 1975

Others have found significant activational effects of androgens on spatial learning and memory through the use of the drug flutamide, an AR antagonist. Intrahippocampal flutamide administration to gonadally intact males impaired learning in the Morris water maze (Edinger & Frye, 2007; Naghdi, Nafisty, & Majilessi, 2001). Naghdi et al. (2001) also demonstrated a detrimental effect of high doses of T (T enanthate) on Morris water maze learning trials in intact males.

Overall, these experiments support the optimal level theory; that is, spatial performance is best when T levels of adult males are moderate.

1.7.2 Activational Effects in Healthy Young Adult Men and Women

In the past 30 years, the effect of T on human spatial performance has received a fair amount of attention, yet the conclusions that can be drawn from this body of work are equivocal. Positive, negative and null relationships, have been documented in mixed sex samples as well as for men and women separately. Even when cognitive tests that elicit a moderate to large effect of sex (e.g., MRT) are used, the effect of T on performance is inconsistent. The impact of androgens on spatial performance in normal adults has been studied primarily through the comparison of groups of individuals and through the use of correlational design. The following sections summarize and table the effects of androgens on spatial performance in healthy young men and women (Tables 2 - 4).

Some authors have demonstrated a positive linear relationship between T and spatial scores in men (Christiansen & Knussmann, 1987; Driscoll et al., 2005;

Hausmann, Schoofs, Rosenthal, & Jordan, 2009; Hooven, Chabris, Ellison, & Kosslyn, 2004; Silverman, Kastuk, Choi, & Phillips, 1999), and that higher T may be associated with a male-typical approach to navigation (e.g., use of cardinal directions; Choi & Silverman, 2002).

Contrarily, higher T has been associated with relatively poor spatial performance in men (Gouchie & Kimura, 1991; Moffat & Hampson, 1996; Neave & Menaged, 1999; and Shute et al., 1983).

At least one placebo-controlled study has documented the effects of T administration in a small group of young, eugonadal men. After receiving T enanthate weekly for two months, performance on the WAIS-R Block Design test significantly decreased (O'Connor, Archer, Hair, & Wu, 2001).

Finally, authors have also reported nonsignificant effects of androgens on a variety of spatial tasks in men (Burkitt et al., 2007; McKeever et al. 1987; McKeever & Deyo, 1990; Puts et al., 2010).

In women, some reports have concluded that higher T levels are associated with relatively superior spatial performance (Burkitt, Widman, & Saucier, 2007; Gouchie & Kimura, 1991; Moffat & Hampson, 1996, Neave & Menaged, 1999; and Shute et al., 1983).

Two studies have experimentally manipulated T in women by administering T (a single sublingual .5 mg dose) . Four hours after T administration, improvement was observed on a delayed recall test of object location memory (Postma, Meyer, Tuiten, van Honk, Kessels, & Thijssen, 2000). In a double-blind placebo-controlled study, MRT

scores improved four to five hours after administration of a single sublingual .5 mg T dose (Aleman, Bronk, Kessels, Koppeschaar, & van Honk, 2004).

Others have reported a nonsignificant effect of T (Choi & Silverman 2002; Driscoll et al, 2005; Hassler, Gupta, & Wollmann, 1992; Hausmann et al., 2009; Karadi et al., 2006; McKeever 1987; Puts et al., 2010; van Anders & Hampson, 2005).

Studies of eugonadal young adult men and women offer inconclusive evidence as to the relationship between T and spatial performance. Examining results from the female samples only, we are left with two possibilities: (a) relatively high T levels are beneficial for women's spatial performance, or (b) no relationship exists between T and spatial performance in this population. Examining results from the male samples leads to three possibilities: (a) relatively high T levels are beneficial for men's spatial performance, (b) relatively *low* T levels are beneficial, or (c) no relationship exists between T and spatial performance in this population. When men and women were combined for analysis, three studies supported the OLT; that is, the best spatial performance is associated with an optimum level of T which is near the high normal end of the female distribution and low normal end of the male distribution (Gouchie & Kimura, 1991; Moffat & Hampson, 1996; and Shute et al., 1983).

1.8 Limitations - Activational Effects of Androgens on Spatial Performance

The variability in results relating T to spatial performance could stem from a number of factors, including: (a) daily and seasonal variation in T, (b) sexual orientation, (c) variation in cognitive scores across the menstrual cycle, (d) method of androgen measurement, and (e) the interaction between T and androgen receptors. The present study directly addressed the latter three.

1.8.1 Effects of Menstrual Phase and Hormonal Contraceptives on Spatial Cognition

Natural variation in estradiol across the female menstrual cycle is a factor to be considered here because nearly a dozen studies have found that women perform better on spatial measures like the MRT during menses than they do during the mid-luteal phase when estradiol is relatively high (for review, see Hampson, 2008). Furthermore, women taking hormonal contraceptives typically have estradiol levels at least as low as naturally cycling women during menses (e.g., DeLeo, Lanzetta, Vanni, D'Antona, & Serveri, 1991). Effects of hormonal contraceptives on spatial scores have also been reported (for review, see Hampson, 2008). In addition to decreasing endogenous estradiol concentrations, hormonal contraceptives decrease free and total T by up to 60% (Wiegratz, Hoffmann, & Kuhl, 1995). For these reasons, it is important to control for both the menstrual phase and for the use of hormonal contraceptives. This can be done in a number of ways, including the exclusion of women who are using hormonal contraceptives coupled with the inclusion of only women who are in the menstrual phase of their cycle.

1.8.2 Method of Androgen Measurement

A second source of variability unique to measuring the effects of androgens on human cognition is the method of specimen collection and measurement of T. Overwhelmingly, studies of T's effects on spatial performance have collected saliva as a specimen and used radioimmunoassay (RIA) to quantify free T. This method provides a relatively noninvasive and inexpensive means of measuring free T.

A number of disadvantages of RIA (e.g., cross-reactivity with compounds similar to T influences specificity) have been cited (e.g., Griffin & Auchus, 2004; Rosner, 2001;

Vermeulen, Verdonck, & Kaufman, 1999). Most importantly is the inadequate precision and sensitivity with which RIA measures T in women (e.g., Demers, 2008; Stanczyk, 2006). Another concern is that RIA can overestimate or underestimate T concentrations (e.g., Wang et al., 2004) compared to a "gold standard" mass spectrometry method. RIAs generally overestimate T in women (e.g., Taieb et al., 2003; Wheeler & Lowry, 1987) and underestimate it in men (e.g., Taieb et al., 2003).

Taieb et al. (2003) measured serum T with 10 immunoassays and mass spectrometry in a sample of men, women, and children. The authors concluded that use of direct RIA such as the popular Coat-A-Count to measure T in eugonadal men is acceptable; however, using any of the commercial assays to get accurate, reliable measures of T in women and children is unadvisable. Mass spectrometry methods are considered the "gold standard" because they can precisely identify and quantify the chemical and structural properties of hormones even when a hormone is present in minute quantities.

The Endocrine Society recommends mass spectrometry techniques for the measurement of T (Rosner et al., 2007); however, the debate regarding adequate measurement of T continues. A recent paper has demonstrated correlations of .67 to .79 between measurements of total T by LC-MS/MS and measurements of total T via RIA in women with PCOS (Legro et al., 2010). It was stated that even LC-MS/MS methods improve in precision at the upper end of the T distribution in hyperandrogenic women. Although the study by Legro et al. (2010) did not include a group of healthy control women, or report on free T, it is reasonable to assume that problems with precision are augmented when it comes to measuring free T in women whose free T

levels are within the normal range. Taken together, these findings strongly support the use of mass spectrometry methods for the measurement of T in eugonadal women.

1.8.3 Androgen Receptor CAG Repeat Number

In order for T to affect spatial learning and memory, AR must be present in the brain to interact with T directly, or indirectly via the conversion of T to DHT. The biological effects that androgens have on brain regions involved in spatial cognition may be mediated by AR activity, concentration, and signaling (e.g., activation of androgen dependent genes) (Brum et al., 2005; Gobinet, Poujol, & Sultan, 2002). Measurement of T or DHT is only one independent variable comprising the interaction between the effects of hormone and receptor on spatial cognition. Therefore, it is of interest to identify a stable marker of androgenicity that is specific to the AR.

One such factor is the AR CAG repeat number (CAGr). The AR CAG repeat is a polyglutamine sequence located on the AR gene of the X chromosome (Xq11-12; Quigley et al., 1995), and the number of repeats is inversely associated with AR transactivation (Chamberlain, Driver, & Miesfeld, 1994; Kazemi-Esfarjani, Trifiro, & Pinsky, 1995). That is, the greater the CAGr, the less the AR transcription, concentration, and signaling (e.g., activation of androgen dependent genes) (e.g., Brum et al., 2005; Chamberlain, Driver, & Miesfeld, 1994; Gobinet, Poujol, & Sultan, 2002; Quigley et al., 1995). The CAGr is polymorphic (Quigley et al., 1995). Normal ranges of the CAGr in men are between eight and 37 with a commonly reported mean of 21 plus or minus two (La Spada, Wilson, Lubahn, Harding, & Fischbeck, 1991; Platz, Rimm, Willett, Kantoff, & Giovannucci, 2000; Rajender, Singh, & Thangaraj, 2007). In women, the normal range of CAGr is between four and 33 (Westberg et al., 2001), and the mean

number of CAGr in one sample of women was 25.9 (Hietala, Sandberg, Borg, Olsson, & Jernström, 2007). Abnormally high CAGr have been associated with androgen insensitivity (Choong, Kemppainen, Zhou, & Wilson, 1996). Relatively high CAGr within the normal range have been associated with infertility (e.g., Tut, Ghadessy, Trifiro, Pinksy, & Young, 1997), genital abnormality (Lim, Nixon, Chen, Hughes, & Hawkins, 2001), and compensatory production of T in males (Huhtaniemi et al., 2009; Krithivas et al., 1999). Fewer CAGr have been associated with PCOS in women (Jaaskelainen, Korhonen, Voutilainen, Hippelainen, & Heinonen, 2005; Shah et al., 2008), physical and social dominance in young men (Simmons & Roney, 2011), and early onset Alzheimer's disease in men (Lehman et al., 2003).

With regard to activational effects of androgens on spatial cognition, it is possible that a meaningful proportion of the participants in previous studies were "incorrectly categorized", and consequently the interpretation of the results is not straightforward. For example, some men categorized as 'low T' in previous studies undoubtedly had relatively fewer CAGr making them functionally moderate or even "high T" men, whereas other men had relatively high CAGr. As CAGr was not measured in any of these studies relating T to spatial cognition, the men with low and high CAGr were placed into the same group based solely on T concentration rather than based on the interaction of T and AR activity, possibly leading to mischaracterization of functional androgen activity.

1.9 Summary of Literature Review and Aims of the Dissertation

The effect of sex on spatial performance ranges from small to large depending on the task. A number of studies reviewed here support the notion that adulthood T

concentrations affect spatial cognition, and that the nature of this hormone-behavior relationship may depend on sex. However, the results taken collectively are equivocal. The incorporation of a number heretofore uncontrolled factors has the potential to at least partially explain the variability in results. Among others, these factors include the use of the most advanced methods of T collection and measurement, and the inclusion of CAGr genotyping as an important individual difference moderator of possible T effects.

The innovation of this project lies in the investigation of how T and CAGr may interact to influence spatial cognition while controlling for several potentially confounding variables and using mass spectrometry, the gold standard of measurement. The primary aim of this study is to investigate the effects of sex, T and CAGr on spatial performance in healthy young adults. It is hypothesized that: (a) men will outperform women on spatial tasks, and (b) testosterone and CAGr will interact to affect spatial cognition outcome variables in both sexes.

CHAPTER 2

METHOD

2.1 Participants

Participants were 88 men (n = 42) and women (n = 46) recruited through WSU online and in-class announcements. Participants were free of self-reported psychiatric and neurological disease, substance abuse, endocrine disorders, heart disease and hypertension, liver and kidney disease, and anemia. Women were normally cycling (i.e., they were not using hormonal contraceptive methods and they reported monthly menstrual periods) and tested during self-reported menses. Four women reported that their menstrual phase ended more than two days before the session, and these women were excluded from analysis. Volunteers were scheduled to participate in individual two-hour sessions at the Clinical Research Center, and were compensated $25.00 or awarded extra course credit. The mean age of the males was 22.48 (3.56) years and the females 22.20 (3.67) years. The males had a mean of 15.05 (1.53) years of education and the females had 14.63 (1.45) years. A wide range of academic majors was represented; approximately half the sample was drawn from a social science, social work, or education program. Half of the sample self-identified as White/Caucasian; 24% as Black/African American; 22% as Asian, 1% as biracial, 1% as "other", and 1% chose not to respond to the item inquiring about race. Eighty percent of the sample self-identified as heterosexual, six percent as bisexual, three percent as homosexual, one percent as “none”, and 10 percent did not respond to the item inquiring about sexual orientation (Table 5).

2.2 Procedure

Phone interviews were conducted to screen volunteers for eligibility. To control for circadian and ultradian effects on T level (e.g., Dabbs, 1990), 79.5 percent of the participants arrived at the laboratory at either 8:30AM or 10:00AM to begin testing. Eighteen participants were scheduled at other times throughout the day for practical purposes (e.g., they had class or worked in the morning). After providing informed consent, participants completed a health and demographics form and four questionnaires regarding their computer and navigation experience. Venipuncture was performed using a BD Vacutainer® Safety-Lok™ Blood Collection Set to obtain 24 mL of blood from the antecubital region. For genotyping purposes, 4 mL of blood was drawn into a plastic whole blood tube spray-coated with EDTA and delivered to the WSU Applied Genomics Technology Center . For the hormone assays, blood was collected into two 10mL glass whole blood tubes, and centrifuged for 15 minutes at 3500 rpm (Thermo Scientific Sorvall Legend X1R) . Serum was aliquoted into 2mL cryovials and stored at -80 degrees C (Thermo Scientific Revco Elite Plus). Another questionnaire was completed before starting the cognitive testing. Next, participants completed five spatial and three non-spatial cognitive tests and the virtual navigation tasks. The simulator sickness questionnaire and another regarding their sense of presence in the virtual environment was completed. The average duration of the data collection session was 114 (18.24) minutes.

2.3 Questionnaires

Questionnaires related to navigation, computer, and computer/video game experience were administered in the following order: the Computer Experience

Questionnaire; an assessment of computer and video game experience; the Santa Barbara Sense of Direction Scale (Hegarty, Richardson, Montello, Lovelace, & Subbiah, 2002), a measure of environmental spatial abilities; the Wayfinding Strategy Measure (Lawton, 1994), a measure of strategy used to navigate to unfamiliar locations; and the Spatial Anxiety Scale (Lawton, 1994), an assessment of anxiety related to navigation behavior. Additional questionnaires included the Immersive Tendencies Questionnaire (Witmer & Singer, 1996) and the Presence Questionnaire (Witmer, Jerome, & Singer, 2005) assessments of the subjective sense of presence (i.e., "being there") in an environment.

2.4 Cognitive Tests

The neuropsychological tests were administered in the following order: Card Rotations Test part 1 (Ekstrom, 1976), a visuospatial test of two-dimensional mental rotation; the Paper Folding Test (Ekstrom et al., 1976), a test of spatial visualization; the Advanced Vocabulary Test (Ekstrom, 1976), a test of vocabulary; the Mental Rotations Test (Vandenberg & Kuse, 1978), a visuospatial test of three-dimensional mental rotation; the Road Map Test of Direction Sense (Money, Alexander, & Walker, 1965), a test of left-right discrimination which requires mental rotation and egocentric perspective; Digit Span forward and backward (Wechsler, 1981), a test of working memory, attention and concentration; the Block Design subtest of the Wechsler Adult Intelligence Scale (Wechsler, 1981), a test of three-dimensional blocks reconstruction; the Controlled Oral Word Association Test (Benton & Hamsher, 1976), a test of phonetic word fluency; and the Card Rotations Test part 2 (Ekstrom, 1976).

2.5 Spatial Navigation Assessments

All virtual environments were designed using Unreal Tournament and Unreal Editor software (Epic Games Inc.). Participants viewed all virtual assessments on a 27.5 inch flat panel LCD monitor approximately 25 inches in front of them, therefore, covering approximately 58 degrees of visual angle. Movement through the virtual environments was controlled with a joystick. The Unreal software automatically collected (x,y) path coordinates every 10 milliseconds, and computed time and distance to completion of each trial as well as overhead views of the participant's path during each trial. In addition, path intersections were tallied and mapped by this program each time a participant intersected an (x,y) coordinate space they had previously traversed; that is, an intersection was the point where the (x,y) coordinates for two paths was the same. This variable was included to calculate the number of times a participant intercepted their own path, effectively returning to an identical point in space that they had already visited.

2.6 Joystick Practice

During joystick practice, the experimenter demonstrated how the joystick worked and then asked participants to navigate to several objects within a virtual room and to traverse a long winding hallway. The purpose of this practice was to familiarize participants with use of the joystick and computer interface.

2.6.1 vMWT – Practice

Prior to completing the learning trials, participants received training to familiarize them with the specific procedures and goals of the vMWT. Participants were given three practice trials of the vMWT in which they were placed in a virtual pool of water enclosed

within a larger room. The room had a ceiling, floor, five walls and four objects placed around the pool, which can serve as navigation cues. The walls can serve as distal geometric cues because they are asymmetric and do not all form 90° angles. Within the pool there was a hidden platform that the participants were instructed to find. When the person "swam" over the hidden platform, it raised them out of the water for 10 seconds rendering them immobile except for the ability to rotate 360 degrees. The platform remained in the same location across all trials and participants were informed of this. They were instructed to find the platform, remember its location, and return to the platform as quickly as possible on each trial. If a participant failed to locate the hidden platform in the allotted three minutes, the experimenter took control of the joystick and located the platform.

2.6.2 vMWT – Learning

Participants were introduced to a new vMWT with seven walls and six objects and were instructed to locate the hidden platform as quickly as possible. They were informed that the platform would remain in a fixed location, although their starting point would be randomized. They were instructed to find the platform as quickly and accurately as possible on all subsequent trials. Similar to the practice trials, they remained on the platform for 10 seconds each time they found it, and were able to rotate 360 degrees during this time. There was a three-minute time limit applied to each of the 10 learning trials. If a participant failed to locate the hidden platform in the allotted three minutes, the experimenter took control of the joystick and located the platform. In all, two men and three women required experimenter completion of one of the 10 trials. One woman required experimenter completion of three trials. Dependent variables

included time and distance taken to reach the hidden platform in each trial, and path intersections.

2.6.3 vMWT – Probe

Following the 10 learning trials, there was one, 60-second, probe trial in which the platform was removed from the pool (same pool as learning trials) unbeknownst to participants. Starting point for the Probe trail was randomized across the three non-goal quadrants. The dependent measures included percentage of time and distance spent in the goal quadrant, number of platform area intersections, and number of path intersections.

2.6.4 vMWT –Visible Platform

In the final vMWT trial, participants were placed in the same pool they had been in for the learning and probe trials. This time the platform location was marked with flags and the participants was told to swim to it as quickly as possible across three trials. Starting point for the Visible Platform trial was randomized. This trial served as an assessment of visuomotor control without requiring spatial cognition and memory in locating the platform. The dependent measures included average time and distance to complete the three trials.

2.6.5 vMWT - Overhead Maps

Following the vMWT trials, three separate overhead diagrams of the vMWT environment were presented to participants (Figure 2). The first of the diagrams contained only the walls; the second, only the objects; and the third was of the vMWT arena as it was presented with all object and geometric cues. In each of these three conditions, participants were told to place an “x” in the pool where they believed the

center of the platform existed during the vMWT trials. The center of their “x” was used to measure the distance in millimeters from the actual center point of the square platform. That distance, for each of these three conditions was used as a dependent variable assessing spatial memory as a function of cue type.

2.6.6 vMWT Strategy Assessment

After the completion of all vMWT trials, participants were asked an open-ended question about how they found the platform and remembered its location. Responses were recorded by the experimenter, and categorized (yes or no) according the following variables: (a) use of proximal cues (cues close to the edge of the pool), (b) use of distal cues (outer walls of pool arena), (c) use of two or more cues at a time, and (d) use of a Cartesian strategy (e.g., they mentioned forming grids or angles with walls and/or objects) to locate hidden platform. Responses were coded by a second rater for the purpose of inter-rater reliability, and agreement was 100% for use of proximal cues, 94% for number of cues, 93% for use of distal cues, and 92% for use of a Cartesian strategy. The primary experimenter's data were used during analysis.

2.7 Simulator Sickness Symptom Questionnaire

After completion of the virtual navigation tasks, participants responded to a 16-item questionnaire that asks about the presence and severity of motion sickness symptoms such as nausea and headache.

2.8 Genomic Analysis

Blood was drawn into 4mL plastic whole blood spray-coated EDTA tubes, The polymerase chain reaction technique, which provided number of AR CAG repeats per participant, was performed at the WSU Applied Genomics Technology Center using the

method stated below (from Dorothy Catella, WSU Applied Genomics Technology Center).

DNA was isolated from blood using a Qiagen EZ1 Advanced. The outer amplification was carried out in a 15 µl reaction containing 20 µmol/l of the gene specific primers NED-gcgcgaagtgatccagaa and gttgctgttcctcatcca (Rosa et al, 2006), 1X True Allele PCR Mix (Applied Biosystems), and 25 ng genomic DNA. The amplification was performed on a Mastercycler Gradient thermocycler (Eppendorf). The reaction conditions were 95^0C for 10 minutes, and amplification was achieved by 40 cycles of 95^0C for 30 seconds, 60.6^0C for 30 seconds, and 72^0C for 30 seconds followed by a final extension of 72^0C for 10 minutes. The NED-labeled PCR products were mixed with LIZ-labelled GeneScan™ 500 size standard (Applied Biosystems) and electrophoresed on a AB3730 (Applied Biosystems). The data were analyzed with GeneMapper (Applied Biosystems). CEPH 1347-02 DNA (Applied Biosystems) was used as a standard DNA and amplified and electrophoresed on each 96-well plate.

Male samples and female homozygous samples at the CAG gene were excluded from the X-inactivation analysis. The remaining heterozygous female samples were analyzed for X-inactivation by assessment of methylation status using the methylation sensitive restriction enzyme *Hpa*II (New England BioLabs® Inc., Ipswich, Massachusetts).

Nonmethylated (active X) DNA segments digest with enzyme and are thereby unavailable for PCR amplification. Methylated (inactive X) *Hpa*II sites do not digest with enzyme and remain intact for amplification. Postdigestion PCR products therefore represent methylated (inactive X) DNA sequences only (Hickey et al, 2002).

225 ng (25 ng/ul) genomic DNA aliquots were either digested with *Hpa*II (5U) or mock-digested in digestion buffer with no enzyme. Samples were digested for 1 hour at 37℃ in a 20 ul reaction volume, with a heat inactiva tion step of 20 minutes at 65℃. Aliquots of 1 ul were amplified by PCR and followed the above CAG method of analysis. Total peak heights for both alleles were calculated for digested and undigested samples. Differences in the ratios of the peak heights between the digested and undigested samples represent the degree to which one allele is more or less methylated than the other in a sample.

2.9 Hormone Assessment

Testosterone analysis was provided by Quest Diagnostics using turbulent flow liquid chromatography tandem mass spectrometry (LC-MS/MS). This method shows no cross-reactivity with 30 steroid compounds biochemically similar to T, has an analytical sensitivity of 1.0 ng/dL, and a reportable range of 1.0 ng/dL to 2000 ng/dL. Free T was calculated based on total and percent unbound to SHBG and albumin.

2.10 Missing Data and Data Transformations

Missing cognitive data included: two Road Map number correct, four Road Map time to completion, one Digit Span, one Blocks Design, and one COWA. Missing values were replaced using expectation maximization (EM), which yielded the same values as using mean substitution (Tabachnick & Fidell, 2001).

Missing questionnaire data included: two SBSOD, one Wayfinding, one SAS, one Immersive Tendencies, five Presence, and three Simulator Sickness. All but three of the Presence and all three of the Simulator Sickness missing values were replaced using

mean substitution. The data that remain missing were from three individuals who did not complete the vMWT (see below).

Two women and one man did not complete the vMWT, and their data were treated as missing. One woman fainted during the blood draw and was not asked to attempt the virtual tasks after the episode. A second woman arrived late and left early due to a schedule conflict. One man terminated his participation early because he felt fatigued. CAGr and hormone data are missing for four participants due to failure of the blood draw.

LG10(X) transformations were used to reduce skew on the Road Map time to completion, distance travelled across the 10 vMWT learning trials, distance travelled across the three vMWT visible platform trials and number of path intersections during the probe trial. Number of correct responses on the Road Map was negatively skewed; a LG10(K-X) transformation reduced the skew. This transformation was computed by subtracting all of the Road Map correct scores from 31 (i.e., 1 plus the absolute value of the maximum score possible for Road Map correct). Values that result from this transformation are greater than zero. Number of path intersections across the 10 vMWT learning trials were positively skewed; LG10(X+1) transformations were used to reduce skew. The LG10(X+1) transformation was applied rather than the LG10(X) transformation because two participants did not intersect their own paths at all during the learning trials (i.e., their scores on that variable were 0); therefore, it was necessary to add a constant of 1 All data transformations were computed based on the summary of "common data transformations" (Tabachnick & Fidell, 2001).

CHAPTER 3

RESULTS

Sections 3.1 to 3.3 present sex differences in cognitive, vMWT, and questionnaire scores; 3.4 to 3.5 describe the hormone concentrations of the sample, as well as relationships between free T and cognitive, vMWT, and questionnaire scores; 3.6 describes the CAGr distribution as well as relationships between CAGr and cognitive, vMWT, and questionnaire scores; and 3.7 presents relationships between free T and cognitive, vMWT, and questionnaire scores by sex and CAGr group.

In the present sample, 80 percent of the participants self-identified as heterosexual, six percent as bisexual, three percent as homosexual, one percent as "none", and 10 percent did not respond to the item inquiring about sexual orientation. To test the possibility that sexual orientation or the interaction of sex and sexual orientation affected the test scores in this study, heterosexuals and those who did not respond to the orientation item were coded as one group, and those who identified as homosexual, bisexual, or "none" were coded as a second group. All analyses were run including and excluding participants who explicitly endorsed an orientation other than heterosexual. Unless otherwise noted, results based on the whole sample are reported.

3.1 Sex Differences – Cognitive Tests

Sex differences on the cognitive measures were investigated with independent samples *t* tests. Males outperformed females on the Money Road Map time to completion, t (81) = 4.34, $p < .001$. When individuals who self-identified as non-heterosexual were excluded, males still outperformed females on the Money Road Map time to completion, t (73) = 4.84, $p < .001$; Money Road Map number of correct

responses, *t* (73) = 2.14, p < .04; and MRT, *t* (73) = 2.01, p < .05. Tables 6 and 7 display the means, standard deviations, and effect sizes (Cohen's *d*) for the cognitive measures as a function of sex, and does not include data from the non-heterosexuals.

3.2 Sex Differences – Virtual Morris Water Task

3.2.1 Visible Platform Trial

Total distance travelled to complete the three trials of the joystick control task did not differ by sex, *t* (77) = 1.40, p = .17.

3.2.2 Learning Trials

Distance travelled across the 10 learning trials was entered into a repeated measures ANOVA with sex as the between subjects factor. Main effects of trial; F (9, 693) = 59.36, p < .001; and sex, F (1, 77) = 3.97, p = .05, *d* = .31 on distance traveled across the learning trials were observed (Figure 3). The sex by trial interaction was not significant, F (9, 693) = 1.55, p = .13. Inclusion of video game experience as a covariate eliminated the significance of the sex effect, F (1, 76) = 1.02, p = .32. When the participants who self-identified as non-heterosexual were excluded, the addition of video game experience as a covariate did not diminish the sex effect, F (1, 69) = 6.21, p < .05.

Number of path intersections across the 10 learning trials were entered into a repeated measures ANOVA with sex as the between subjects factor. The main effects of trial, F (9, 693) = 16.81, p < .001 and sex, F (1, 77) = 12.37, p = .001, *d* = .63 were significant, with women intersecting their own path more frequently than men. (Figure 4). The interaction of trial and sex was not significant, F (9, 693) = 1.08, p = .37. Inclusion of video game experience as a covariate did not diminish the significance of the sex effect, F (1, 76) = 6.29, p = .01.

3.2.3 Probe Trial

Men travelled a greater distance during the probe trial than women, $F(1, 77) = 20.60$, $p < .001$; travelled a greater distance in the goal/platform quadrant of the pool; $F(1, 77) = 21.47$, $p < .001$; and crossed the platform area more frequently, $F(1, 77) = 10.38$, $p = .001$. The sex difference in platform areas crossings was significant in the first 30 seconds of the probe trial, $F(1, 77) = 20.64$, $p < .001$, but not in the second 30 seconds, $F(1, 77) = .84$, $p = .36$. In contrast to the learning trials, men intersected their own path more often than women in the probe trial; $F(1, 77) = 12.28$, $p = .001$, and this was specific to path intersections within the goal quadrant, $F(1, 77) = 9.54$, $p = .003$, as the sexes did not differ in the number of path intersections outside of the goal quadrant, $F(1, 77) = 1.24$, $p = .27$. Adding video game experience as a covariate in an ANCOVA did not diminish the significant effect of sex on any of these variables; however, using total distance travelled as a covariate attenuated the sex effect. Seventy-five percent of the distance travelled in the probe trial by both men and women was within the goal quadrant. Table 8 displays means, standard deviations, and effect sizes for probe trial measures as a function of sex.

3.2.4 Maps

When participants were shown overhead maps of the vMWT and asked to place an "x" where they thought the center of the platform area was, a main effect of map type on accuracy of marking the platform location was observed, $F(2, 152) = 66.48$, $p < .001$. Post-hoc comparisons revealed differences between all three map types with participants being most accurate on the map with all of the cues (mean error = 8.43mm, SD = 6.12mm), intermediate with the map containing all proximal object cues (mean

error = 7.37mm, SD = 5.40mm), and least accurate with the map that contained only distal cues (mean error = 22.93mm, SD = 16.44mm). Regarding the map that contained only distal cues, participants who reported using distal cues to locate the platform across learning trials were more accurate than those who did not utilize distal cues, $F(1,76) = 6.54$, $p = .01$; and women were more accurate than men, $F(1, 21) = 9.82$, $p = .005$.

3.2.5 Strategy

After completion of all virtual navigation tasks, participants were asked to report how they found the hidden platform and remembered its location. Participants reported using one to four cues (mean = 2.24, SD = .83) while locating and remembering the location of the hidden platform across learning trials. All participants reported using at least one proximal cue, 29 percent reported use of at least one distal cue, and 44 percent were categorized based on their self-reported strategy as employing a Cartesian strategy. The percentage of participants who reported using at least two cues to locate the platform did not differ by sex, $\chi^2 (1, N = 79) = 3.31$, $p = .07$. The percentage of participants who reported using distal cues did not differ by sex, $\chi^2 (1, N = 79) = .10$, $p = .75$. The percentage of participants who were classified as using a Cartesian strategy to locate the platform did not differ by sex, $\chi^2 (1, N = 79) = .64$, $p = .42$ (Table 9).

Follow-up analyses were performed to test the main effect of Cartesian strategy, and interaction of strategy and sex, on vMWT performance. Univariate ANOVA was conducted with sex and Cartesian strategy as independent factors and each of the vMWT measures as dependent variables. There was no main effect of strategy on any of the vMWT performance variables. A significant interaction between sex and strategy

was found for accuracy of platform area identification on the overhead map which contained only distal cues, $F (1, 79) = 5.24$, $p < .05$ (Figure 5). Men and women who were classified as not using a Cartesian strategy showed a negligible difference in accuracy, whereas women who were classified as using a Cartesian strategy demonstrated greater accuracy. Given that use of a Cartesian strategy did not necessarily involve use of distal cues, a follow-up analysis included only the individuals who reported using at least one distal cue to locate the hidden platform. The sex by strategy interaction was attenuated, $F (1, 19) = 1.73$, $p = .20$, but the main effect of sex remained significant, $F (1, 19) = 6.82$, $p < .05$. The use of video game experience as a covariate did not diminish the female advantage in this analysis.

3.3 Sex Differences – Computer, Game, and Navigation Experience

To investigate sex differences in video game and navigation experience, independent samples *t* tests were performed. Men reported more video game experience than women; CEQ, $t (81) = 3.57$, $p < .001$; ITQ-Games, $t (81) = 2.70$, $p = .008$. Table 10 displays the means, standard deviations, and effect sizes (Cohen's *d*) for the video game and navigation experience questionnaires as a function of sex.

3.4 Hormone Concentrations

Men had higher free T concentrations than women, $t (40.53) = 18.71$, $p < .001$. Testosterone levels did not differ significantly by season in men, $F (3, 35) = .34$, $p = .80$; or women, $F (3,32) = 1.10$, $p = .37$. Testosterone levels did not differ significantly by time of day in men, $F (2, 39) = .77$, $p = .80$; or women, $F (2, 36) = .49$, $p = .62$; a result which was due to the constraints placed on time of testing. Table 11 displays means, standard deviations, minimum and maximum values, and the normal reference range

(Quest Diagnostics) as a function of sex. Table 11 also displays T values by time of day and season. Two men and three women were excluded from analyses relating testosterone with behavior because their free T levels were at least two standard deviations above the mean for their sex.

3.5 Relationships between Free Testosterone and Cognitive, vMWT, and Questionnaire Variables

Linear and quadratic relationships between free T and cognitive, vMWT, and questionnaire variables were tested for men and women, and were duplicated without the non-heterosexual participants. Where the exclusion of non-heterosexuals changed the relationship between free T and cognitive, vMWT, or questionnaire score, results will be reported. Figures 6 - 9 display the scatter plots for significant linear and quadratic relationships between free T and cognitive, vMWT, and questionnaire scores in women. Tables 12 - 14 display all bivariate correlations between free T and cognitive, vMWT, and questionnaire scores respectively. Data from participants determined to be univariate or multivariate outliers are not represented in the tables.

3.5.1 Relationships between Free T and Cognitive, vMWT, and Questionnaire Scores in Men

Free T was not significantly related to any of the cognitive, vMWT, or questionnaire measures in men.

3.5.2 Relationships between Free T and Cognitive, vMWT, and Questionnaire Scores in Women

Free T was positively associated with performance on the Digit Span Forward test, $R^2 = .13$, $F(1, 36) = 6.54$, $p = .02$, and negatively related to time to complete the

Road Map, R^2 = .15, F (1,35) = 7.12, p = .01. Free T was not significantly related to any of vMWT measures in women. Positive linear relationships were observed between free T and scores on the Computer Experience Questionnaire, R^2 = .17, F (1, 35) = 8.03, p = .008. Quadratic trends fit the data between free T and Spatial Anxiety, R^2 = .19, F (2, 33) = 4.94, p = .01. All relationships between free T and questionnaire scores were attenuated to nonsignificance when non-heterosexuals were omitted from the analysis.

3.6 Androgen Receptor CAG Repeat

AR CAG repeats ranged from 12 to 30 with a mean of 21.06 (3.29) and a median and mode of 21 (Figure 10). Men had an average of 21.32 (3.24) repeats, and women had an average of 20.81 (3.37) repeats. There was no sex difference in repeat number, *t* (82) = .70, p = .49.

For the group as a whole, Pearson correlation coefficients between repeat number and cognitive, vMWT, and questionnaire data were nonsignificant. Significant positive correlations were found between repeat number and Card Rotations, r (40) = .36, p = .02; MRT, r (40) = .31, p = .05; Vocabulary, r (40) = .32, p = .04, and Digit Span Forward, r (40) = .33, p = .04 in women (Figures 11 -13). A negative correlation was observed between CAGr and time to complete the Road Map, r (38) = -.34, p = .03 (Figure 14). An inverted-u shaped quadratic function best fit the relationship between CAGr and SAS for women, R^2 = .11, F (2,37) = 3.17, p = .05 (Figure 15). For men, significant correlations were found between repeat number and CEQ, r (41) = -.36, p = 02; ITQ Total, r (41) = -.31, p = .05; and ITQ-Games, r (41) = -.38, p = .02 (Figures 16 - 18).

3.7 Relationships between Free T and Cognitive, vMWT, and Questionnaire Scores as a Function of Sex and CAGr

It was hypothesized that the relationship between testosterone and spatial cognition would vary by sex and CAGr (low CAGr vs. high CAGr). To test this prediction, a median split was performed on the CAGr variable, which placed those with 21 or fewer repeats in the "low" group and those with 22 or more repeats in the "high" group. Correlations between free T and the cognitive, vMWT, and questionnaire variables were analyzed separately for low and high CAGr groups within each sex.

3.7.1 Relationships between Free T and Cognitive Scores as a Function of Sex and CAGr

Correlations between free T and the cognitive variables ranged from near zero to an absolute magnitude of .49 when men and women were categorized by low or high CAGr; however, none of these correlations were statistically significant. When non-heterosexual men were excluded from the analysis, four of the correlations between free T and spatial measures in the low CAGr group increased in magnitude: Card Rotations, $r(16) = -.51$, $p = .03$; Block Design, $r(16) = -.46$, $p = .05$; accuracy on the Road Map, $r(16) = .49$, $p = .03$; and Paper Folding, $r(16) = -.52$, $p = .02$. In the high CAGr group, the correlation between free T and Paper Folding score was positive, $r(16) = .58$, $p = .02$. The significant zero order correlations between free T and Paper Folding scores in the high versus low CAGr groups were subjected to a Fisher r-to-z transformation, and found to be significantly different from each other, $z = 3.03$, $p = .002$. Figures 19 - 27 display the results, with significant correlations noted with an asterisk.

3.7.2 Relationships between Free T and vMWT Scores as a Function of Sex and CAGr

None of the correlations between free T and vMWT outcome measures by sex and CAGr group were significant. Figures 28 - 33 display the results.

3.7.3 Relationships between Free T and Questionnaire Scores as a Function of Sex and CAGr

For women in the high CAGr group, free T was positively associated with video game experience, r (16) = .53, p = .03. When non-heterosexuals were excluded, higher free T was correlated with lower Spatial Anxiety scores in the men with low CAGr, r (15) = -.46, p = .05. Figures 34 - 40 display the results, with significant correlations noted with a star.

CHAPTER 4

DISCUSSION

The purpose of this project was to assess the impact of sex, T, and CAGr on spatial performance in a group of healthy young adults. The hypothesis that men would outperform women on traditional measures of spatial cognition, as well as a computerized version of the Morris Water Task was supported. Most importantly, this initial investigation suggests that CAGr may have a direct impact on cognition and may modify the relationship between T and spatial cognition within sex.

4.1 Effect of Sex on Cognitive and vMWT Measures

The male advantage on measures of spatial cognition reported here is congruent with several reviews and meta-analyses (Hyde, 1981; Linn & Petersen, 1985; Maccoby & Jacklin, 1974; and Voyer et al., 1995), as well as individual studies similar to the present study (e.g., Gouchie & Kimura, 1991; Moffat & Hampson, 1996; Nowak & Moffat, 2011; Silverman et al., 1999).

The sex difference favoring men in vMWT performance is also in agreement with previous reports (Astur et al., 1998; Astur, Tropp, Sava, Constable, & Markus, 2004; Burkitt, Widman, Saucier, 2007; Driscoll, Hamilton, Yeo, Brooks, & Sutherland, 2005; Mueller, Jackson, & Skelton, 2008; Nowak & Moffat, 2011; Rahman & Koerting, 2008; and Sandstrom, Kaufman, & Huettel, 1998). It is noteworthy that the large male advantage on distance travelled in the goal area of the probe trial, platform area crossings, and number of path intersections was attenuated when *percentage* of total distance travelled within the goal area was used as the dependent variable. This is similar to a study by Driscoll et al. (2005) in which no effect of sex was found on

percentage of distance spent in the goal quadrant during the probe trial. Astur et al. (1998) observed that men located the hidden platform faster than women across learning trials, and travelled a greater percentage of their total distance in the goal quadrant during the probe trial. Both Astur et al. and Driscoll et al. used a version of the vMWT which contained only distal cues, so it is possible that our task with its multiple proximal cues is easier. In support of the notion of task difficulty, men in Astur's study travelled 60% of their total probe trial distance in the goal quadrant, while the men and women in our task spent 75% of their total distance within the goal area.

Contrary to prediction was the observation of a female advantage in locating the platform area in the Map Wall condition (i.e., the overhead map that contained only distal cues). Women whose self-reported platform-locating strategy was classified as Cartesian outperformed the rest of the sample. Because this map included only distal cues, and one could use a Cartesian strategy without integrating distal cues, the analysis was run again using only those individuals who mentioned at least one distal cue as part of their strategy. The female advantage, regardless of strategy, was upheld even after matching men and women for use of distal cues. Past research has found that men were able to use distal geometric cues to find the hidden platform in the vMWT whereas women did not effectively use these cues and were successful only when stable landmarks were available to aid relocation of the hidden platform (Sandstrom et al., 1998). Likewise, women forced to use a Euclidean strategy to navigate a university campus made more errors than men, and more errors than women who were forced to use a landmark-based navigation strategy (Saucier et al., 2002). The strength of these two studies lies in the fact that they manipulated strategy, whereas the present study

coded the self-reported strategy as either Cartesian or not. However, unlike the studies of Saucier at al. (2002) and Sandstrom et al. (1998), the environment in the present study remained stable over the trials and participants were free to utilize all of the object and distal wall cues. Participants responded to the open-ended question: "How did you find and remember the location of the platform?". Women reported using fewer cues than men to locate and remember the platform location, but this does not negate the possibility that women observed and remembered more cues than they used. It is possible that the female advantage on this map is due to a tendency for women to outperform men on tasks of object location memory, such as memory for the relative position of objects within an array (Eals & Silverman,1994; McBurney, Gaulin, Devineni, & Adams, 1997; and Silverman & Eals, 1992). A limitation of the study is that an assessment of memory for the individual vMWT cues was not administered. It is also worth noting that the sex difference favoring females occurred only on the mapping component after all virtual environment learning, probe and swim trials had been completed. Regardless of the cause of the sex difference on the mapping task, it was not reflected in the preceding learning or probe trials of vMWT task which favored males.

4.2 Effect of Testosterone on Cognitive and vMWT Measures

In considering our findings regarding free T in isolation from CAGr, our results are not commensurate with the optimal level theory (i.e. negative effect of relatively high T in men, and positive effect of high T in women; Gouchie & Kimura, 1991; Moffat & Hampson, 1996; and Shute et al., 1983); or with reports of a positive effect of T in men (Christiansen & Knussmann, 1987; Driscoll et al., 2005; Hausmann, Schoofs,

Rosenthal, & Jordan, 2009; Hooven, Chabris, Ellison, & Kosslyn, 2004; Silverman, Kastuk, Choi, & Phillips, 1999), and women (Aleman et al., 2004; Burkitt et al., 2007; Gouchie & Kimura, 1991; Moffat & Hampson, 1996, Neave & Menaged, 1999; Postma et al., 2000; and Shute et al., 1983). Instead, our findings are most similar to studies which have found null or at least nonsignificant relationships between T and spatial scores in men (Burkitt et al., 2007; Choi et al., 2002; Christiansen & Knussman, 1987; Gouchie & Kimura, 1991; Hassler et al., 1992; McKeever et al., 1987, 1990; and Puts et al., 2010), and women (Driscoll et al., 2005; Gouchie & Kimura, 1991; Hassler et al., 1992; Hausmann et al., 2009; Karádi et al., 2006; McKeever et al., 1987; Puts et al., 2010; Shute et al., 1983; and van Anders et al., 2005).

Correlations between free T and vMWT performance in our study ranged in magnitude from .05 to .25 and did not reach statistical significance. Two other studies have assessed the effects of free T on men's and women's performance in a vMWT (Burkitt et al., 2007; and Driscoll et al., 2005). Driscoll et al. reported that higher T was associated with faster performance across learning trials of a vMWT in men, but that T was not significantly related to performance in women. Burkitt et al. found that women in their low T group took longer to locate the hidden platform across learning trials than men in the low and high T groups, as well as women in the high T group. Men in the low and high T groups did not differ in vMWT performance. A major limitation of this (Burkitt et al.) study was an error in sample collection or immunoassay method that led to a mean salivary T level of 96.7 pg/mL in women classified as high T; an average value that far exceeds the reference range for healthy young women.

One advantage of the present study was its use of multiple assessments of spatial skills and experience. In women, higher T was associated with faster performance of the Money Road Map test, an assessment of left-right discrimination in a mapping context which required mental rotation and egocentric perspective. Higher T was also correlated with better scores on the Digit Span Forward test, an assessment of working memory, attention, and concentration. These two results are consistent with the notion that higher T may be associated with better cognitive scores in women, however we did not replicate this relationship with tests of mental rotation or spatial visualization.

The present study differed in four key ways from those that preceded it. First, we controlled for menstrual cycle effects on spatial performance by testing women during menses, a phase of the cycle associated with relatively superior mental rotation scores (for review, see Hampson, 2008). This is likely a contributing factor to the medium effect of sex on MRT score in the present study compared to the larger sex effect reported in studies where menstrual phase was uncontrolled (e.g., Moffat & Hampson, 1996; Nowak & Moffat, 2011; Silverman et al., 1999). Likewise, women in our sample were not taking hormonal contraceptives, which are known to suppress T levels by up to 60% (Wiegratz et al., 1995). Hormonal contraceptive use can also impact spatial performance (Hampson, 2008). Third, we did not screen potential participants based on sexual orientation but we did address the possibility of a sex by sexual orientation interaction on all measures by duplicating analyses without the individuals who self-identified as non-heterosexual. Finally, we collected blood samples to quantify T by LC-MS/MS, the accepted “gold standard” for T measurement (e.g., Rosner et al., 2007), as opposed to collecting saliva samples and quantifying T via RIA.

Of the 18 studies reviewed in this paper (Tables 2 & 3), 12 collected saliva and quantified T by immunoassay (primarily RIA). The other 6 collected blood samples and measured T from serum or plasma using RIA. Advantages of these methods are that collection of saliva is more convenient and less invasive than drawing blood, and RIA is less expensive than mass spectrometry. The primary disadvantage is the lack of precision at the low end of the T distribution (i.e., eugonadal women). Immunoassay methods such as RIA have been shown to overestimate T in women (e.g., Taieb et al., 2003; Wheeler & Lowry, 1987) and underestimate it in men (e.g., Taieb et al., 2003; Wang et al., 2004). The Endocrine Society recommends mass spectrometry techniques for the measurement of T (Rosner et al., 2007); however, the debate regarding adequate measurement of T continues, especially where it concerns young adult eugonadal women.

Of the studies that supported the optimal level theory (Burkitt et al., 2007; Gouchie & Kimura, 1991; Moffat & Hampson, 1996; and Shute et al., 1983), limitations in the method of salivary sample collection or T measurement exist in three. Inadequate specificity of the RIA used in the study by Shute et al. (1983) led to cross-reactivity with compounds biochemically similar to T. The saliva-stimulating gum used by Gouchie and Kimura (1991) interfered with the RIA and resulted in unreasonably high T levels (e.g., a mean free T concentration of 51.10 pg/mL in women). The study by Burkitt et al. (2007) experienced a similar problem with their assay which resulted in the mean free T level of women exceeding 96 pg/mL. Free T concentrations reported by Moffat and Hampson (1996) were within the normal range for salivary free T.

Silverman et al. (1999) conducted a study very similar to the one by Moffat and Hampson (1996),and even took care to use the same laboratory for their salivary RIA analyses. Silverman et al. reported a positive linear correlation between free T and MRT scores in men, whereas Moffat and Hampson reported a negative linear relationship. As reported by Silverman et al., the "sole salient difference" between the two studies was that the men in the study by Moffat and Hampson had a higher mean MRT score than the men in their sample. Silverman speculated that the correlation between T and MRT scores could be modified by how difficult the MRT was for the participants, assuming that accuracy was a reflection of difficulty. Silverman et al. went on to suggest that higher T may have been beneficial for their participants because the MRT was perceived as challenging, whereas high T could have shown the opposite effect in the higher scoring sample of Moffat and Hampson because the MRT may have been perceived as an easy task. According to this logic, a sample of men with lower accuracy rates than those of Silverman's sample should also exhibit a positive correlation between free T and MRT scores. The men in a study by Hausmann et al. (2009) had accuracy rates on the MRT that were approximately 3% lower than those of Silverman's participants, and a positive correlation was reported. On the other hand, according to Silverman's speculation, a sample of men with higher accuracy rates than those reported by Moffat and Hampson should exhibit a more pronounced negative correlation between free T and MRT scores. Accuracy on the MRT in the present study was comparable to that of the men in Moffat and Hampson's study, as was the range of free T values (approximately 40 - 140 pg/mL). In our sample of men, T levels did not relate significantly to MRT scores. It does not appear to be the case that the

discrepancy in results between Moffat and Hampson, Silverman et al., and the present study can be easily explained by task accuracy/difficult, although with only 3 studies, it is difficult to resolve this issue definitively. A future study could address Silverman's idea more systematically.

4.3 Effect of CAGr on Cognitive, vMWT, and Questionnaire Measures

On account of inconsistencies in the literature relating T to spatial cognition, we added another measure of androgenicity. While T fluctuates based on time of day, season, phase of the menstrual cycle, behavior, and age, the number of CAG repeats in the AR gene is constant over time in an individual. When an AR is bound by T, the ligand-receptor complex regulates expression of androgen dependent genes throughout the brain and body. CAGr may be thought of as a factor that modifies the individual's capacity for androgenicity along a continuum from low to high. Where on this continuum an individual lies impacts their physical and mental state.

Our study examined linear and nonlinear relationships between CAGr and cognitive, vMWT, and questionnaire variables. Lower androgenicity (higher CAGr) in women was associated with better performance on tests of vocabulary, 2D and 3D mental rotation (Card Rotations and MRT), left-right discrimination which required mental rotation and egocentric perspective (Road Map), as well as working memory, attention, and concentration (Digit Span). The finding that lower androgenicity (higher CAGr) was associated with better mental rotation performance appears to be a direct contrast with predictions that higher T would be associated with better spatial scores in women In men, lower androgenicity (higher CAGr) was associated with less video game experience (CEQ and ITQ-Games) and less of a tendency to become immersed in

activities such as video games (ITQ-Total). However, focusing solely on the bivariate correlations between CAGr and the dependent measures omits any effect of T, and one of the aims of this study was to consider T and CAGr together as a means to explain variability in spatial scores.

4.4 Relationships between Testosterone and Cognitive and vMWT Measures by CAGr and Sex

We also tested the prediction that T and CAGr act dependently in that CAGr may modify the relationship between T and cognitive, vMWT, and questionnaire variables. CAGr was subjected to a median split. Correlations between T and cognitive, vMWT, and questionnaire variables were examined for low and high CAGr groups within sex.

The six correlations that were significant in men were all related to spatial measures. In half of them, higher T was associated with poorer scores on measures of mental rotation and spatial visualization (Card Rotations, Paper Folding, and Block Design) in the low CAGr group, providing support for the idea that too much androgen activity (i.e. high T and low CAGr) can be detrimental to certain domains of spatial cognition. For men in the low CAGr group, higher T levels were associated with lower levels of spatial anxiety, which may be consistent with the recent work demonstrating that men with fewer CAGr tend to be more physically and socially dominant (Simmons & Roney, 2011).

One significant correlation emerged for men in the high CAGr group, and revealed that high T was associated with better Paper Folding scores. In the case of Paper Folding, men in the low and high CAGr groups showed the opposite pattern of association with T as predicted. The joint consideration of CAGr and Free T resulted in

findings that appear broadly consistent with the optimal level theory. For men with moderate androgenicity (high T and high CAGr), T was positively related to performance, but for men with relatively high androgenicity (high T and low CAGr) T was negatively correlated with performance. Negligible bivariate correlations in the male sample between T and Paper Folding, Card Rotations, and Block Design could be explained by the differential relationships within low and high CAGr groups. For example, the bivariate correlation between T and Paper Folding scores in men was .06; however, when men were categorized based on low or high androgenicity (CAGr), correlations that were equal in magnitude but opposite in direction emerged (Figure 20). This observation illustrates that CAGr may play a critical moderating role and the lack of consideration of this genomic variant in androgen/cognition associational studies may lead to erroneous findings and conclusions.

4.5 Conclusion

The primary contribution of this study was the inclusion of CAGr as a measure of androgenicty in addition to free T. This study demonstrated a direct relationship between number of AR CAG repeats and four cognitive measures in women. In men, an interactive relationship was observed in that the association of T with spatial measures depended on whether the participant possessed a low or high number of AR CAG repeats. Caution in interpretation is warranted due to small sample sizes within each CAGr by sex group; however, this initial investigation suggests an interaction between T and CAGr on spatial cognition, especially in men.

4.6 Strengths & Limitations

Strengths of this study include the addition of CAGr as an indicator of androgenicity; use of LC-MS/MS to measure T from blood samples; the control of menstrual phase and hormonal contraceptive use; University-wide recruitment of participants (as opposed to psychology students only); and the inclusion of multiple measures of spatial cognition, video game, navigation strategy, sense of direction, and spatial anxiety experience.

The primary limitation of the present study is the small sample size, especially when broken down by sex and CAGr group. It is possible that some of the effects represent type I error, just as it is possible that true effects were not detected within the sample.

Another limitation was that 10% of the sample did not respond to the item inquiring about their sexual orientation. This presented a problem because we know that orientation, especially in men, impacts spatial performance. Heterosexual men tend to perform better than homosexual men on measures of spatial cognition that favor men (Gladue, Beatty, Larson, & Staton, 1990; McCormick & Witelson, 1991; Neave, Menaged, & Weightman, 1999; Rahman & Wilson, 2003; Sanders & Ross-Field, 1986; Wegestin, 1998), and homosexual men have been found to employ spatial strategies that are more similar to those of women than of men (Rahman, Abrahams, & Wilson, 2003; Rahman, Andersson, & Govier, 2005). Had the sample size been substantially larger, this 10% of the sample could have been excluded. We did not attempt to exclude non-heterosexuals from participation during the screening process. Our solution was to code participants into two groups, one that explicitly identified as non-heterosexual, and one that included self-identified heterosexuals along with the non-

responders. Although the analyses were conducted with and without the non-heterosexual group, this factor should be considered in the design and sample size estimations in the future.

4.7 Future Directions

A pending addition to the present study is the measurement of T via RIA. With these results, we will be able to correlate T obtained from LC-MS/MS methods with those obtained via RIA, and evaluate differences in T based on method within the same sample. The correlation between the two methods is predicted to be stronger in men due to the increased precision of both methods at the higher end of the T distribution. A recent paper has demonstrated a correlation of .67 between measurements of T by LC-MS/MS and measurements of T via RIA in women with PCOS (Legro et al., 2010). The women in the present study were not hyperandrogenic; therefore, it is predicted that a correlation of less than .67 will be found for women. The most important contribution of this upcoming study will be the duplication of analyses and comparison of results within the same sample.

Additionally, the present study should be replicated in a larger sample of men to test the reliability of the interactive effect of T and CAGr on spatial measures. If a study of this nature confirms the pattern displayed here, it would be feasible to offer CAGr group membership (low or high androgenicity) as an explanation for some of the null and discrepant reports of the past. For example, if the present sample of men was limited to those with high androgenicity (low CAGr), the negative linear correlation between free T and spatial scores reported by Moffat and Hampson would be replicated. One additional benefit of the present study is that it provides the basis of a

power analysis to estimate the required sample size to assess the interactive effects of T and CARr on various cognitive measures.

It is also possible that a similar interactive effect would reach statistical significance in a larger sample of women, as we demonstrated a trend in this direction on four cognitive measures. The unexpected negative effect of high androgenicity (low CAGr) on measures of mental rotation could be elucidated by this interaction.

Finally, this research could be applied in the domain of age-related cognitive differences. Testosterone alone has been associated with neuroprotection in men (for reviews, see Driscoll & Resnick, 2007; and Holland, Bandelow, & Hogervorst, 2011), and other researchers have already begun to identify combinations of T and CAGr group membership as risk factors for Alzheimer's disease in older men (Lehman et al., 2003). New research assessing the genetic risk for cognitive impairment in middle-aged participants may benefit from the inclusion of CAGr genomics.

APPENDIX A - TABLES

Table 1

Summary of functional magnetic imaging studies investigating sex differences in brain activation while performing a three-dimensional mental rotation task.

First Author	Sample	Overlap	M > W	W > M
Thomsen et al. 2000	6M, 5F	Bilateral SPL, Bilateral IFG	Rt parietal lobe	Rt IFG
Jordan et al. 2002	10M, 14F	Bilateral SPL, PMdc, Pre-SMA	SOG, MOG	Bilateral SPL, PMdc, Pre-SMA, ITG, Rt IFG
Halari et al. 2006	9M, 10F	Bilateral MTG, Lt MOG, Bilateral SOG, Bilateral SPL, Lt IOG	n.s	n.s
Hugdahl et al. 2006	6M, 5F	Bilateral SPL, Bilateral IFL	Rt parietal lobe	Rt IFG
Weiss et al. 2003	10M, 10F	Bilateral IFG, MFG, SFG, Cingulate gyrus, Bilateral IPL	Bilateral IPG	Bilateral SPL, Rt IFG

Note. F: female, IFG: inferior frontal gyrus, IFL: inferior frontal lobe, IOG: inferior occipital gyrus, IPG: inferior parietal gyrus, IPL : inferior parietal lobe, IPS : inferior parietal sulcus, ITG : inferior temporal gyrus, Lt: left, M: male, MFG : medial frontal gyrus, MOG: medial occipital gyrus, MTG :medial temporal gyrus, n.s.: nonsignificant sex difference, PMdc : caudal region of dorsal premotor area, Rt: right, SMA : supplementary motor area, SOG : superior occipital gyrus, SPL : superior parietal lobe

Table 2

Observational Studies of the Relationship between Testosterone and Spatial Performance in Normal Young Men

First Author (Year of Publication)	Sample Size	Spatial Tests	Measurement: Androgens	Results: Androgens & Spatial Performance
Shute (1983)	12	MPFB	RIA – plasma (androgens)	Lo T > Hi T*
Shute (1983)	43	Spatial Composite	RIA – plasma (androgens)	Linear **(negative), Quadratic, & Cubic
Gouchie (1991)	42	MRT, Paper Folding	RIA – saliva	Paper Folding Lo T > Hi T MRT Lo T = Hi T
Moffat (1996)	40	Spatial Composite	RIA – saliva	Negative
Burkitt (2007)	40	vMWT	ELISA – saliva	vMWT Lo T = Hi T
Neave (1999)	33	MRT	RIA - saliva	Negative
Driscoll (2005)	33	vMWT	RIA - saliva	Positive
Hausmann (2009)	59	MRT	LIA – saliva	Positive
Choi (2002)	46	Route Learning	RIA – saliva	Positively associated with male-typical strategy; Negatively associated with female-typical strategy
Puts (2010)	177	MRT	RIA- saliva	n.s.
Christiansen (1987)	117	Spatial Composite	RIA – serum (T & DHT)	T_{ser} : Positive (4 of 6 tests)

			RIA – saliva	T_{sal} : Positive (1 of 6 tests) DHT: Positive (2 of 6 tests)
Christiansen (1987)	117	Spatial Composite	RIA – serum (T & DHT) RIA – saliva	T_{ser} : Lo < Hi T_{sal} : Lo < Hi n.s. DHT_{ser} : Lo < Hi
Hooven (2004)	27	MRT	RIA – saliva	Positive
Silverman (1999)	64	MRT	RIA – saliva	Positive
McKeever (1990)	58	MPFB, SIBT	RIA – serum	T: n.s. DHT: n.s.
Hassler (1992)	26	Spatial Relations Test	RIA - serum	n.s.
McKeever (1987)	22	MPFB, SIBT	RIA – serum	n.s.

Note. * The symbol “>” is used to mean, for example, that group A had a mean score superior to that of group B (i.e., A > B). The symbol “<” is used to mean, for example that group A had a poorer mean score than group B (i.e., A < B).

Note. ** Negative means there was a negative correlation between the androgen measured and the dependent spatial measure (i.e., high testosterone associated with poor spatial score). Positive means there was a positive correlation between the androgen measured and the dependent spatial measure.

Table 3

Observational Studies of the Relationship between Testosterone and Spatial Performance in Normal Young Women

First Author (Year of Publication)	Sample Size	Spatial Tests	Measurement: Androgens	Mean Androgen Concentrations	Results: Androgens & Spatial Performance
Shute (1983)	12	MPFB	RIA – plasma (androgens)	not available	Lo T < Hi T
Shute (1983)	48	Spatial Composite	RIA – plasma (androgens)	2.3 ng/ml	Positive n.s.
Gouchie (1991)	46	MRT, Paper Folding	RIA – saliva	51.1 pg/ml	Paper Folding Lo T < Hi T MRT Lo T = Hi T
Moffat (1996)	40	Spatial Composite	RIA – saliva	17.9 pg/ml	Positive
Burkitt (2007)	40	vMWT	ELISA – saliva	96.7 pg/ml	vMWT Lo T < Hi T
Neave (1999)	25	MRT	RIA-saliva		Positive
Driscoll (2005)	35	vMWT	RIA-saliva		n.s.
Puts (2010)	160	MRT	RIA- saliva	14.76 - 20.35 pg/ml	n.s.
Hassler (1992)	25	Spatial Relations Test	RIA - serum	.26 ng/ml	n.s.
Hausmann (2009)	55	MRT	LIA – saliva	24 pg/ml	n.s.
Choi (2002)	60	Route Learning	RIA – saliva	16.24 pg/ml	n.s.
McKeever (1987)	23	MPFB, SIBT	RIA – serum	.43 ng/ml	n.s.
van Anders (2005)	99	MRT, Paper Folding, GZSO	RIA – saliva	21 pg/ml*	n.s.
Karádi (2006)	33	Mental Rotation	RIA – saliva	14.4 pg/ml	n.s.

Note. * approximate mean for two samples of women that did not differ in T concentration

Table 4

Effects of Testosterone Administration in Young Adults

First Author (Year of Publication)	Sample	Spatial Tests	Androgen Treatment	Results: Androgens & Spatial Performance
O'Connor (2001)	N = 29 Men (n= 14 experimental, n=15 control)	WAIS-R Block Design	T- 8 weeks	Experimental < Control; Positive correlation between T and Block Design at baseline, but negative correlation after 4 and 8 weeks of T administration
Postma (2000)	N = 15 Women	Object Location Memory	T- single dose	Improvement
Aleman (2004)	N = 14 Women	MRT	T- single dose	Improvement

Table 5.

Participant Demographics

	Men	Women
Age - Mean (SD)	22.48 (3.56)	22.20 (3.67)
Education - Mean (SD)	15.05 (1.53)	14.63 (1.45)
Race (%)		
White/Caucasian	57	43
Black/African American	12	35
Asian	24	20
Biracial	2	0
Other	2	0
No Response	0	2
Sexual Orientation (%)		
Heterosexual	71	87
Homosexual	7	4
Bisexual	0	4
"None"	2	0
No Response	19	4

Note. Education: 12 years = high school, 13 - 16 = college freshman - senior, 17 or more = graduate level. The mean of approximately 15 years for each sex is the equivalent of a junior standing in college.

Table 6

Means, Standard Deviations, and Effect Sizes for Spatial Measures as a Function of Sex

	Cards	Paper	MRT	Map T	Map C	Blocks
Males						
Mean	101.47	6.89	22.82	62.17	27.93	46.00
SD	34.66	5.91	9.23	21.54	2.72	11.17
Females						
Mean	88.71	5.68	18.42	85.81	26.86	42.45
SD	39.73	7.19	8.92	34.42	3.11	12.15
Cohen's *d*	.34	.18	.49*	1.14***	.50*	.30

Note. Road Map number correct (Map C) and time (Map T) to completion were transformed to correct skew, but untransformed means are reported here for ease of interpretation.

*** $p \leq .001$, ** $p \leq .01$, * $p \leq .05$

Table 7

Means, Standard Deviations, and Effect Sizes for Nonspatial Measures as a Function of Sex

	Vocab.	Digits	COWA
Males			
Mean	2.34	18.21	38.34
SD	3.47	4.02	10.02
Females			
Mean	2.53	17.79	42.26
SD	4.83	3.16	10.45
Cohen's *d*	.05	.17	.38

Table 8

Means, Standard Deviations, and Effect Sizes for vMWT Probe Trial Measures as a Function of Sex

	Distance	Distance Goal	X-ings	Inter.	Inter. Goal
Males					
Mean	15003.27	10960.38	6.95	24.38	22.10
SD	4229.50	2821.30	3.16	15.39	14.31
Females					
Mean	10928.11	7950.78	4.77	14.73	13.45
SD	3463.24	2796.82	2.62	9.97	10.58
Cohen's *d*	1.05***	1.07***	.75***	.79***	.69**

Note. Path intersections were transformed to correct skew, but untransformed data are presented here for ease of interpretation. Distance = total distance travelled; Distance Goal = distance travelled in the goal quadrant; Xings = total number of platform area crossings; Inter. = total number of path intersections; Intter. Goal = number of path intersections within the goal quadrant. *** $p \leq .001$, ** $p \leq .01$, * $p \leq .05$

Table 9

Classification of Self-Reported Approach

	Proximal	Distal	Cartesian	2 + Cues
Males				
Yes	40	11	20	36
No	0	29	20	4
Females				
Yes	39	12	16	29
No	0	27	23	10
Total				
Yes	79	23	36	65
No	0	56	43	14

Table 10

Means, Standard Deviations, and Effect Sizes for Video Game and Navigation Experience as a Function of Sex

	CEQ	SBSOD	Orientation	Route	SAS	ITQ
Males						
Mean	5.04	73.05	29.05	16.50	20.08	7.53
SD	1.44	16.23	6.40	3.85	6.07	3.31
Females						
Mean	3.46	67.27	26.65	18.19	20.70	5.05
SD	1.49	14.20	6.27	4.35	5.74	3.07
Cohen's *d*	1.08***	.38	.38	.41	.11	.78**

*** p ≤ .001, ** p ≤ .01, * p ≤ .05

Table 11

Mean, Standard Deviation, Minimum, Maximum, and Reference Range Values for Free T as a Function of Sex, Time of Day, and Season

	Men	Women
Mean (SD)	94.89 (32)	3.27 (2.67)
Minimum - Maximum	35.7 - 201.6	.7 - 13.3
Reference Range	46 - 224	.1 - 6.4
Time of Day		
Early (8:30AM)	88.21 (23.76)	2.81 (1.45)
Late (10:00AM)	93.10 (24.97)	2.28 (.73)
Other	85.35 (10.61)	2.47 (1.55)
Season		
Winter	93.79 (26.02)	2.17 (.98)
Spring	88.15 (19.17)	2.51 (1.43)
Summer	84.79 (27.51)	3.43 (.89)
Fall	94.25 (13.34)	2.10 (.85)

Note. T values are all presented as pg/mL.

Table 12.

Correlations between Free Testosterone and Cognitive Measures in Men and Women, Excluding Outliers on Measures of Free Testosterone and Cognition

	1	2	3	4	5	6	7	8	9	10	11
Men	.03	-.10	.06	-.14	.07	.05	-.04	.05	.03	.15	-.10
Women	.28	.24	.10	.13	-.42**	-.04	.03	.33*	.24	.33*	.02

Note. 1: MRT, 2: Card Rotations, 3: Paper Folding, 4: Block Design, 5: Road Map time to completion, 6: Road Map number correct, 7: Vocabulary, 8: COWA, 9: Digit Span Total, 10: Digit Span Forward, 11: Digit Span Backward

Table 13.

Correlations between Free Testosterone and vMWT Measures in Men and Women, Excluding Outliers on Measures of Free Testosterone and vMWT Variables

	1	2	3	4	5	6	7	8	9	10
Men	-.07	-.11	-.01	.10	.11	-.05	.10	-.21	-.14	-.25
Women	-.13	-.06	-.11	-.16	-.10	.11	-.19	.06	.20	.21

Note. 1: Total Distance - Learning Trials, 2: Total Number of Path Intersections - Learning Trial, 3: Total Distance - Probe Trial, 4: Distance in the Goal Quadrant - Probe Trial, 5: Platform Area Crossings - Probe Trial, 6: Total Number of Path Intersections - Probe Trial, 7: Total Distance - Visible Platform Trial, 8: Error - Map All Cues, 9: Error - Map Object Cues, 10: Error - Map Distal Cues

Table 14.

Correlations between Free Testosterone and Questionnaire Measures in Men and Women, Excluding Outliers on Measures of Free Testosterone and Questionnaire Variables

	1	2	3	4	5	6	7	8
Men	.09	.09	-.20	-.02	-.10	-.02	-.08	-.14
Women	.40*	.31	-.29	.16	-.27	.03	.37*	.00

Note. 1: Computer Experience Questionnaire, 2: Santa Barbara Sense of Direction, 3: Spatial Anxiety Scale, 4: Wayfinding Strategy -Orientation, 5: Wayfinding Strategy - Route, 6: Immersive Tendencies Total, 7: Immersive Tendencies - Games, 8: Presence - Total

APPENDIX B - FIGURES

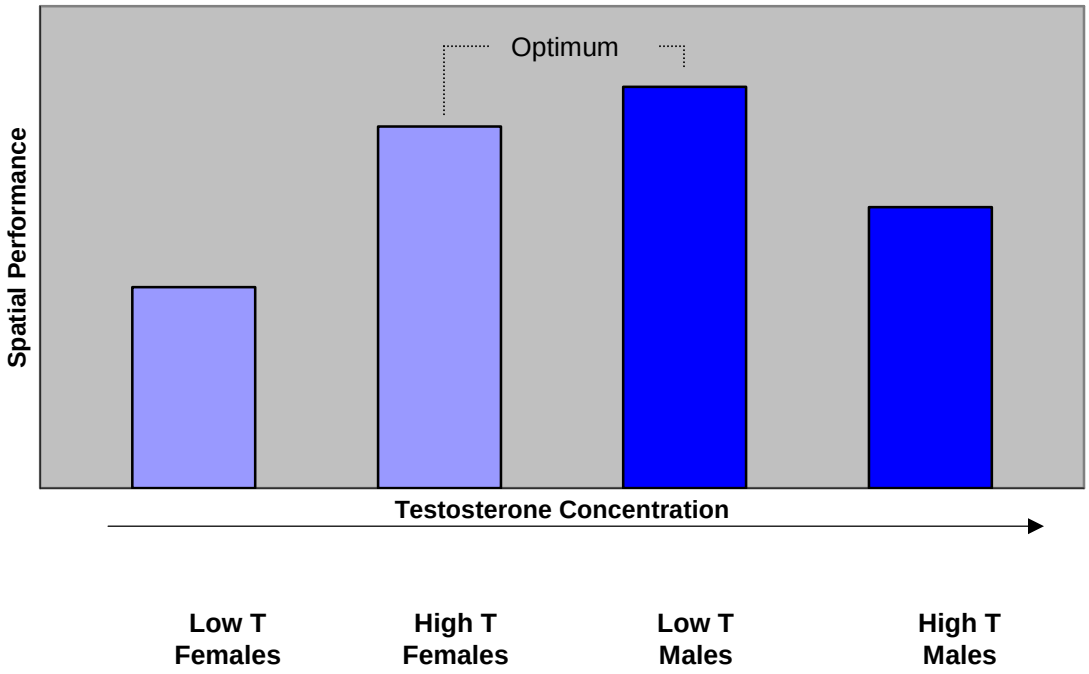
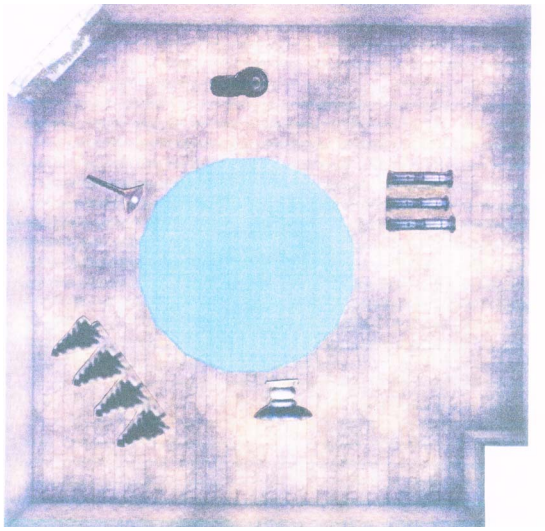
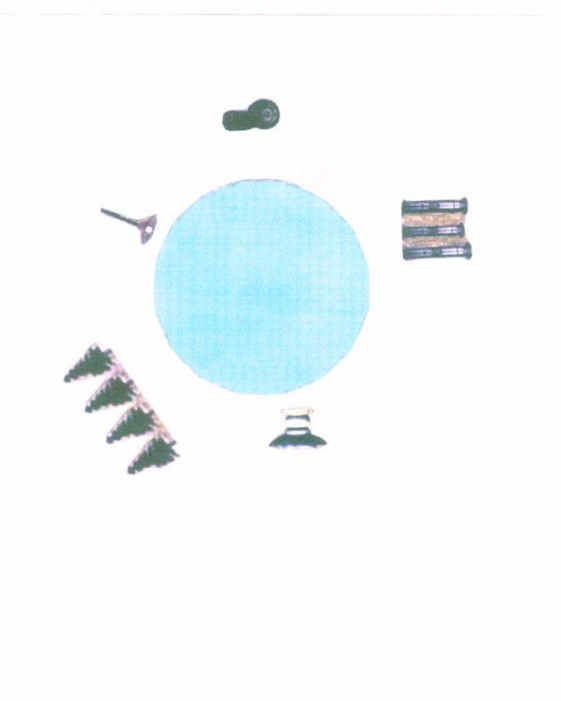


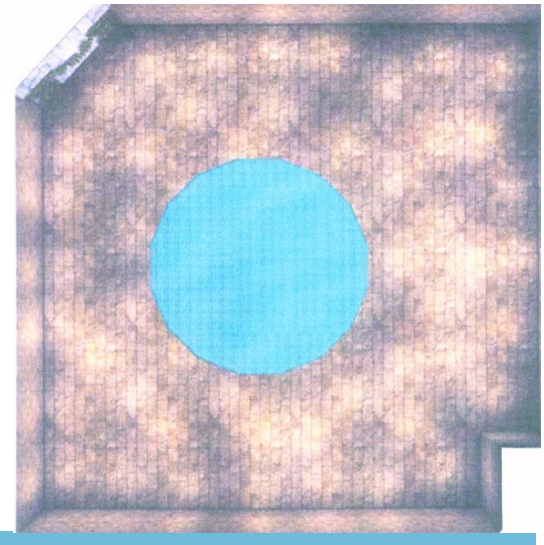
Figure 1. Optimal level theory. This figure is a theoretical representation of the nonlinear relationship between testosterone concentration and spatial performance based on the studies of Shute et al. (1983), Gouchie and Kimura (1991), and Moffat and Hampson (1996). These authors suggest there may be a testosterone level that corresponds with optimum spatial performance. The x-axis represents, from left to right, increasing testosterone concentration. Each column represents a group of individuals based on sex and testosterone concentration. The y-axis represents, from bottom to top, increasingly superior spatial performance (e.g., mental rotations). The text “Optimum”, and the associated dotted lines, represent the range of testosterone hypothesized to correlate with superior spatial skills.



Map All – Contains all cues available during vMWT trials



Map Obj – Contains proximal object cues available during vMWT trials



Map Wall – Contains distal cues available during vMWT trials

Figure 2 .Three overhead views of the vMWT as presented in the cognitive mapping conditions: (top to bottom) Map All, Map Obj, and Map Wall. Participants were asked to place an “x” where they believed the center of the platform was located in the vMWT learning trials.

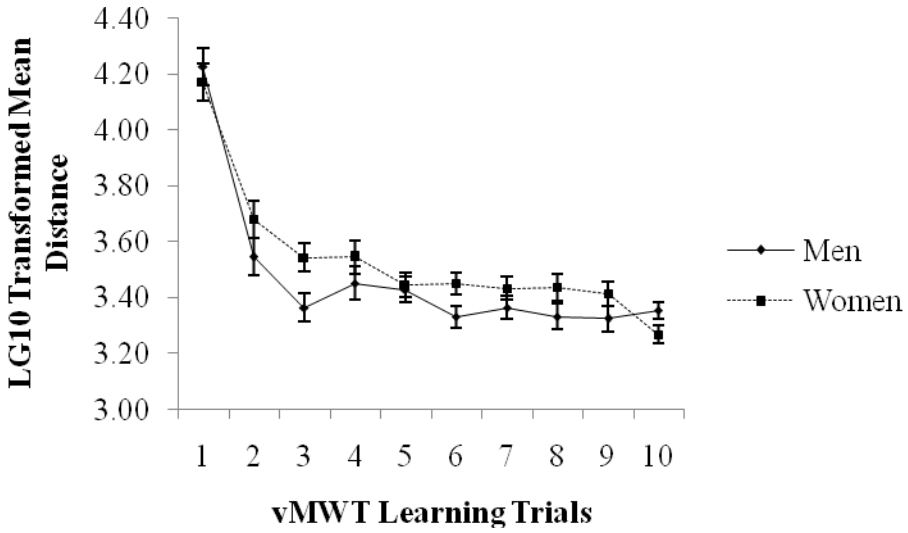


Figure 3. LG10 transformed distance travelled across the 10 vMWT learning trials for men and women separately. There was a significant sex difference in which men traveled a shorter distance than women.

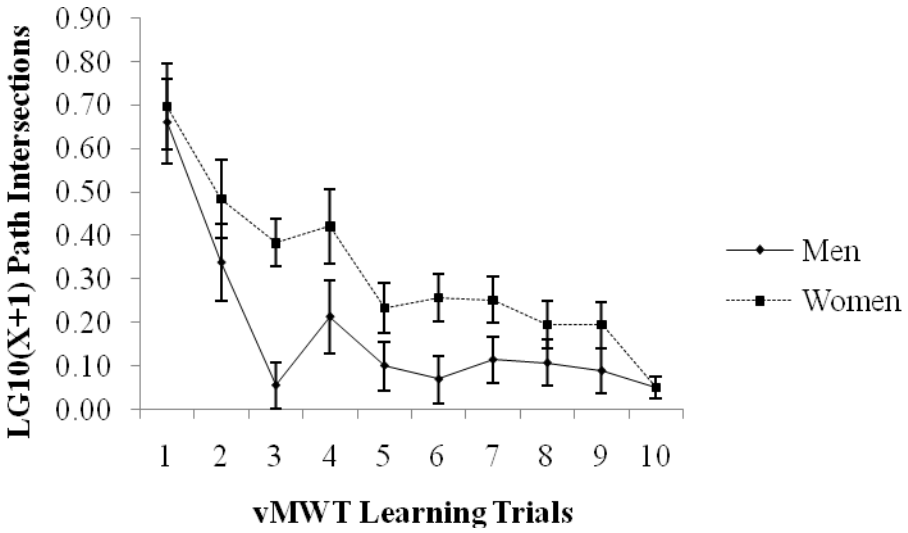


Figure 4. LG10(X=1) transformed number of path intersections made across the 10 vMWT learning trials for men and women separately. There was a significant sex difference in which men had fewer path intersections than women.

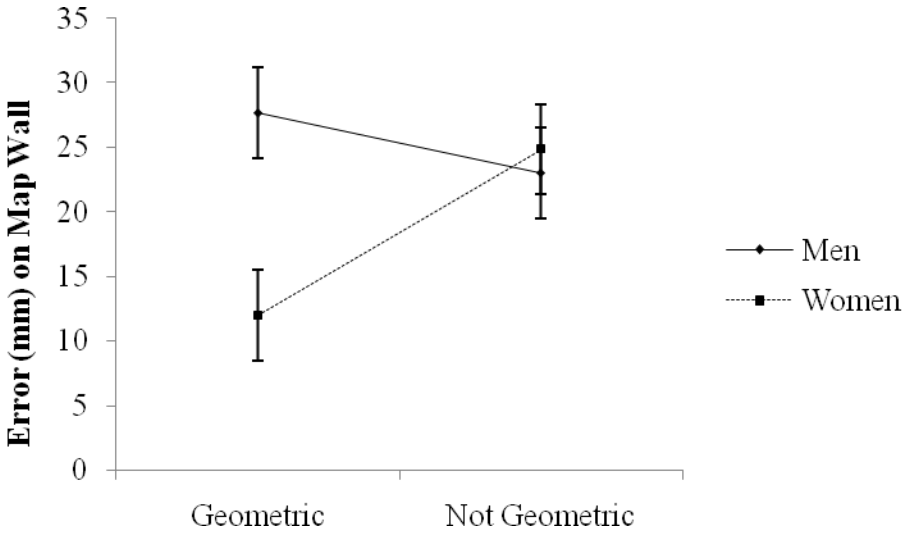


Figure 5. Sex by strategy interaction on error in placement of the platform area in the overhead map condition that contained only the distal room cues (Map Wall). Women whose self-reported strategy was coded as "geometric" showed the least error on this task.

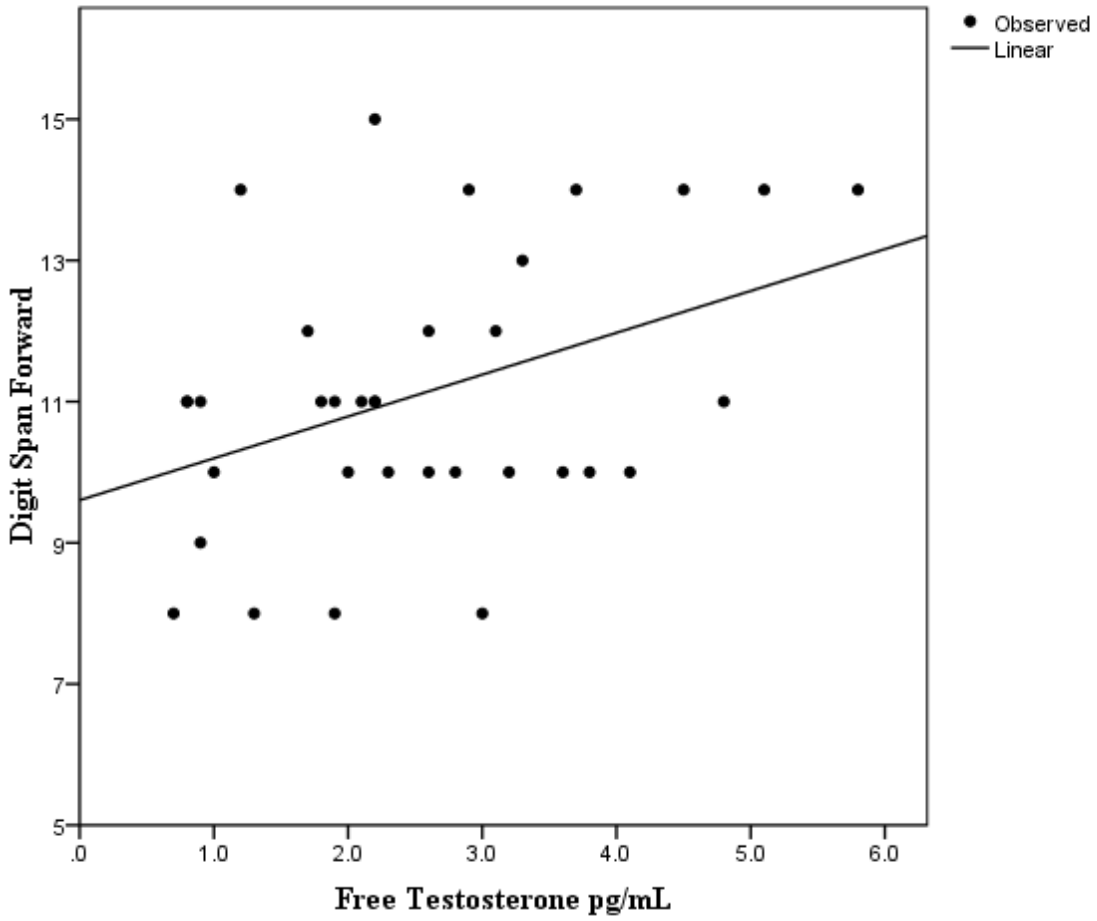


Figure 6. A positive linear relationship between free T and Digit Span Forward scores was observed in women.

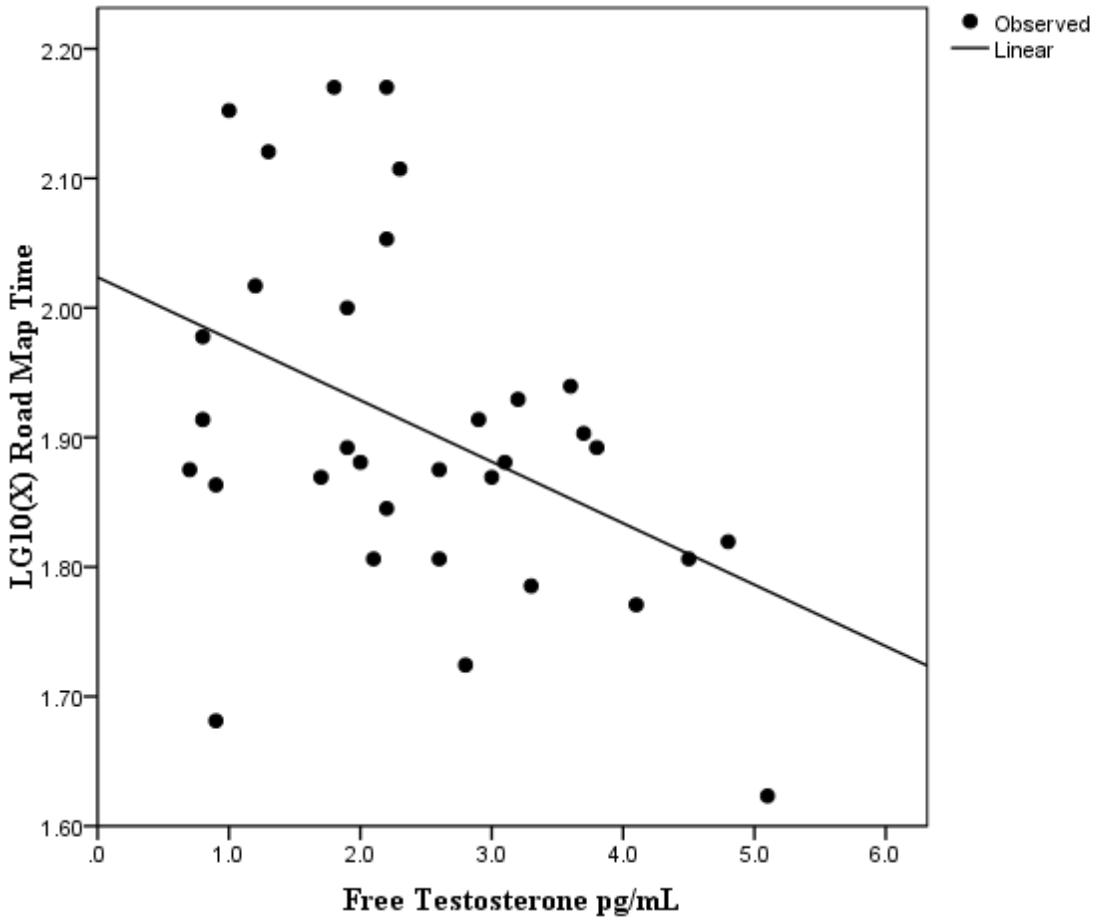


Figure 7. A negative linear relationship between free T and time to complete the Money Road Map Sense of Direction test was observed in women.

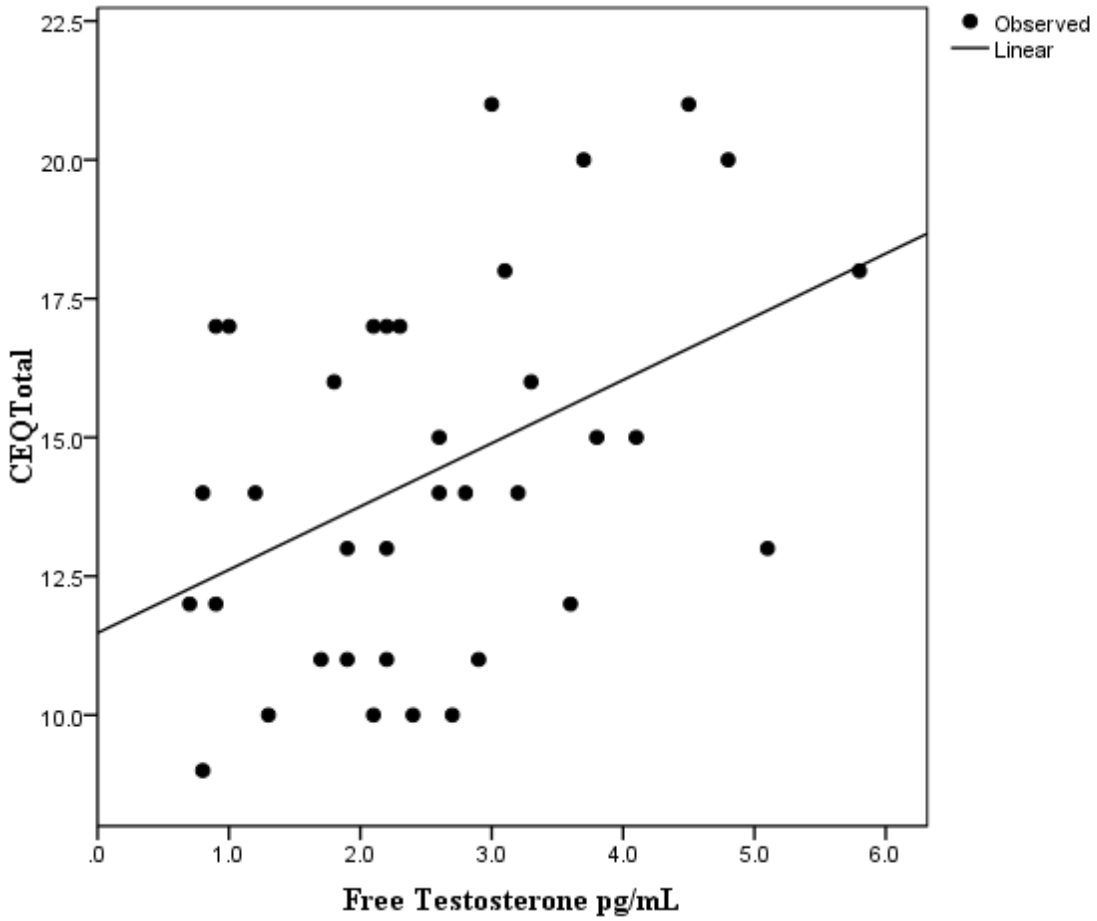


Figure 8. A positive linear relationship between free T and CEQ scores was observed in women.

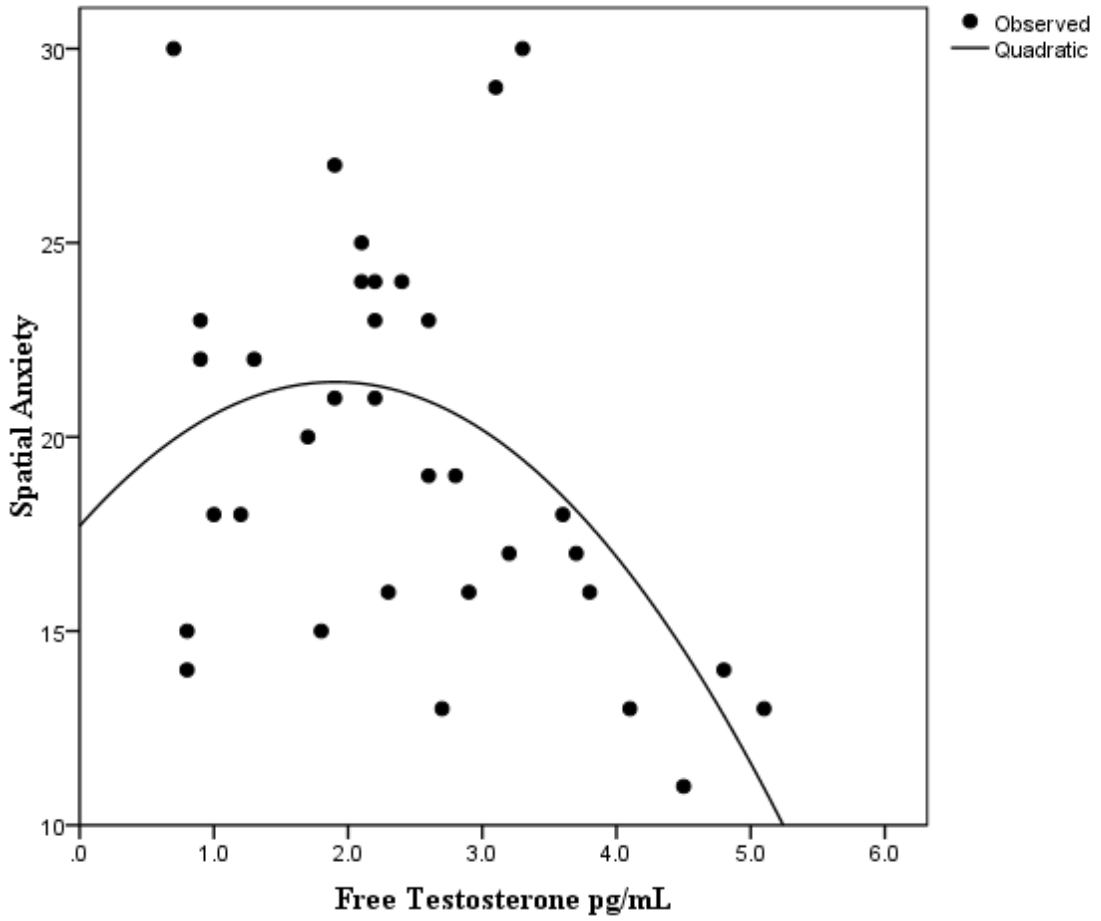


Figure 9. A quadradic relationship between free T and Spatial Anxiety scores was observed in women.

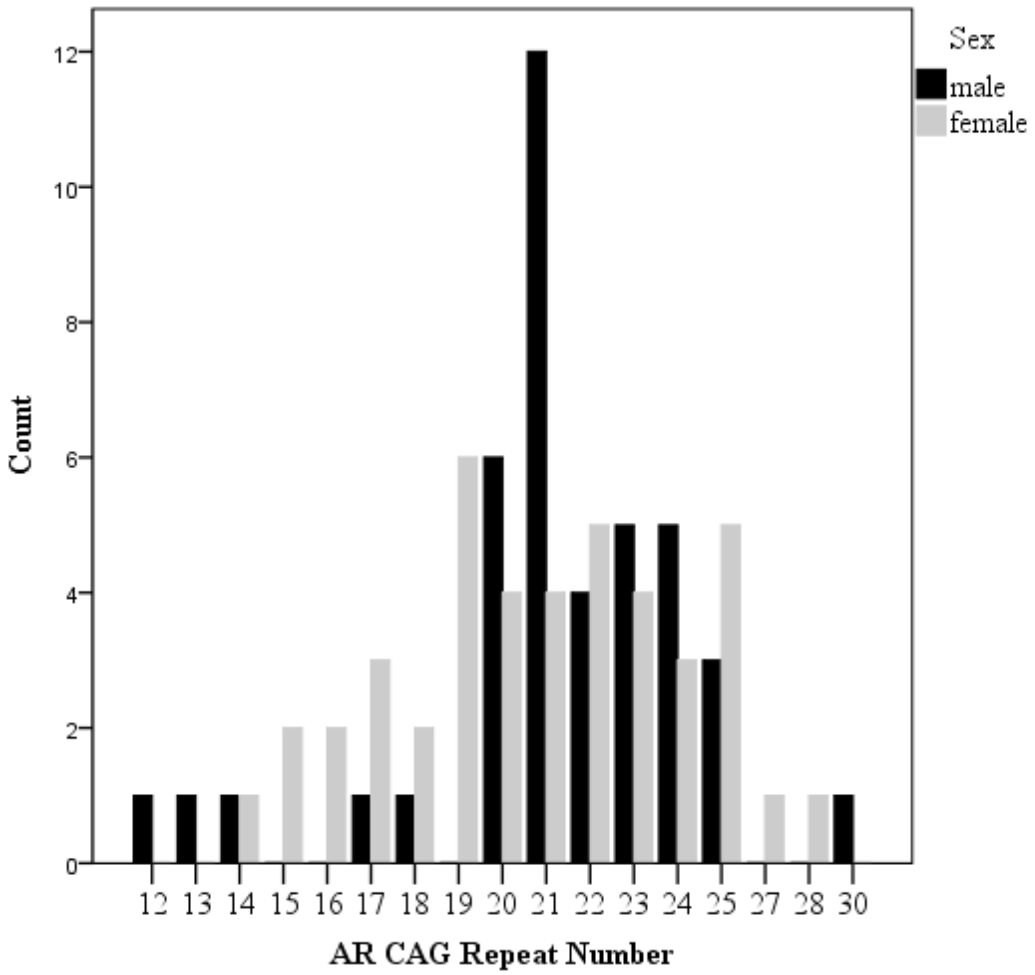


Figure 10 . Distribution of AR CAG repeat number for men and women. AR CAG repeats ranged from 12 to 30 with a mean, median and mode of 21. There was no sex difference in number of repeats.

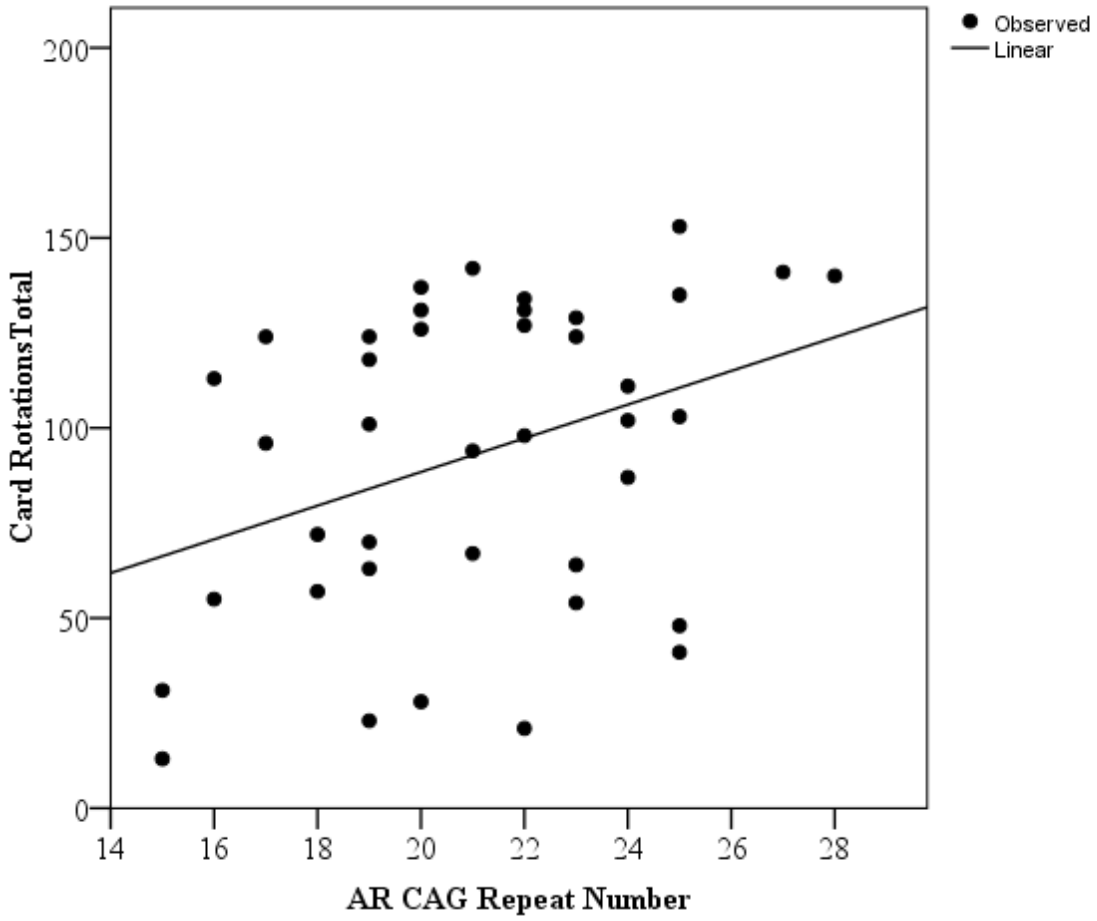


Figure 11. A positive linear correlation was found between CAGr and Card Rotations scores in women.

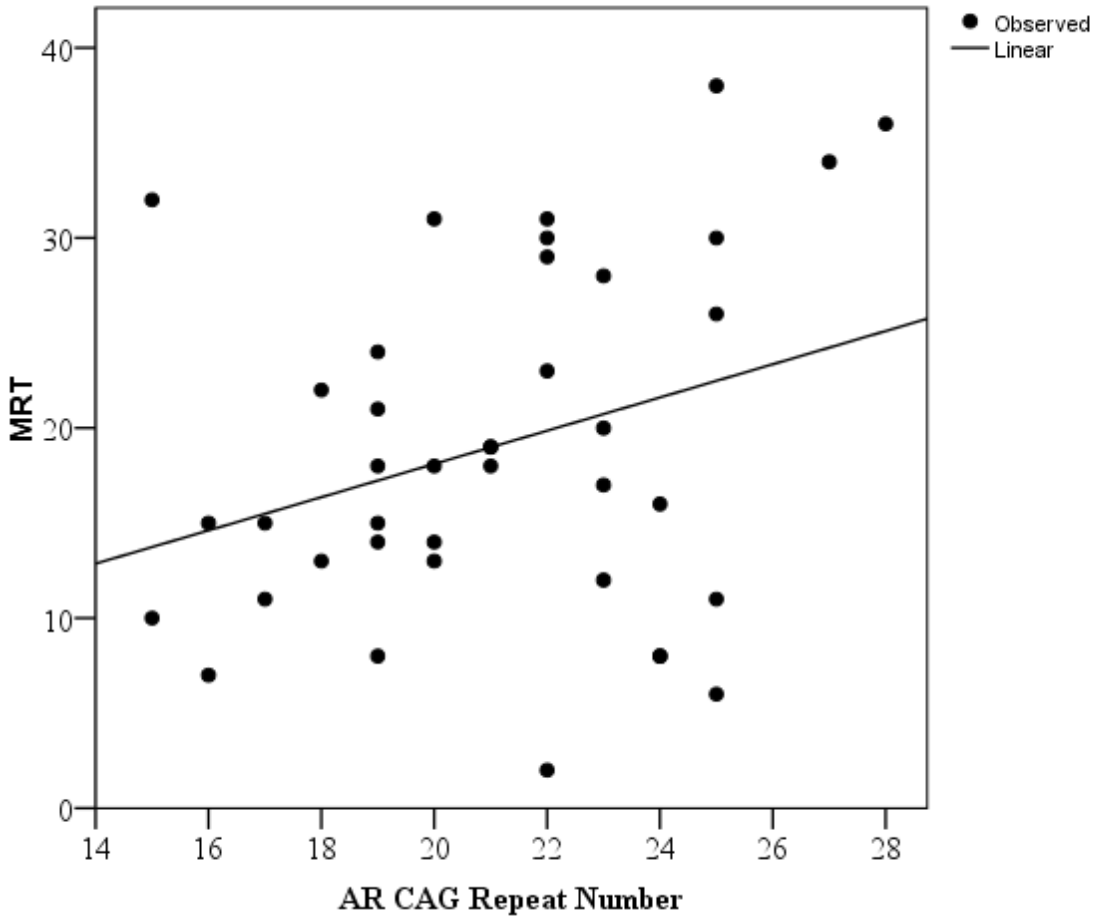


Figure 12. A positive linear correlation between CAGr and MRT scores was observed in women.

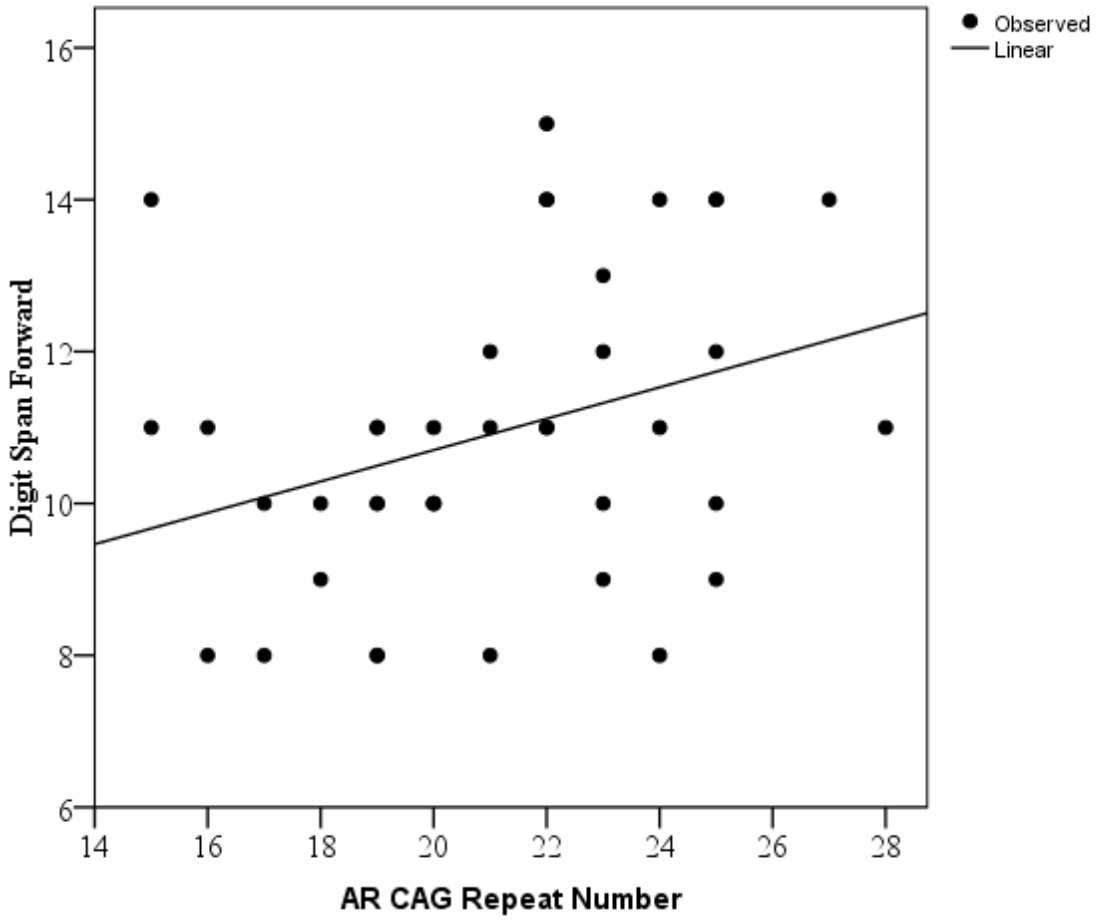


Figure 13. A positive linear correlation between CAGr and Digit Span Forward scores was observed in women.

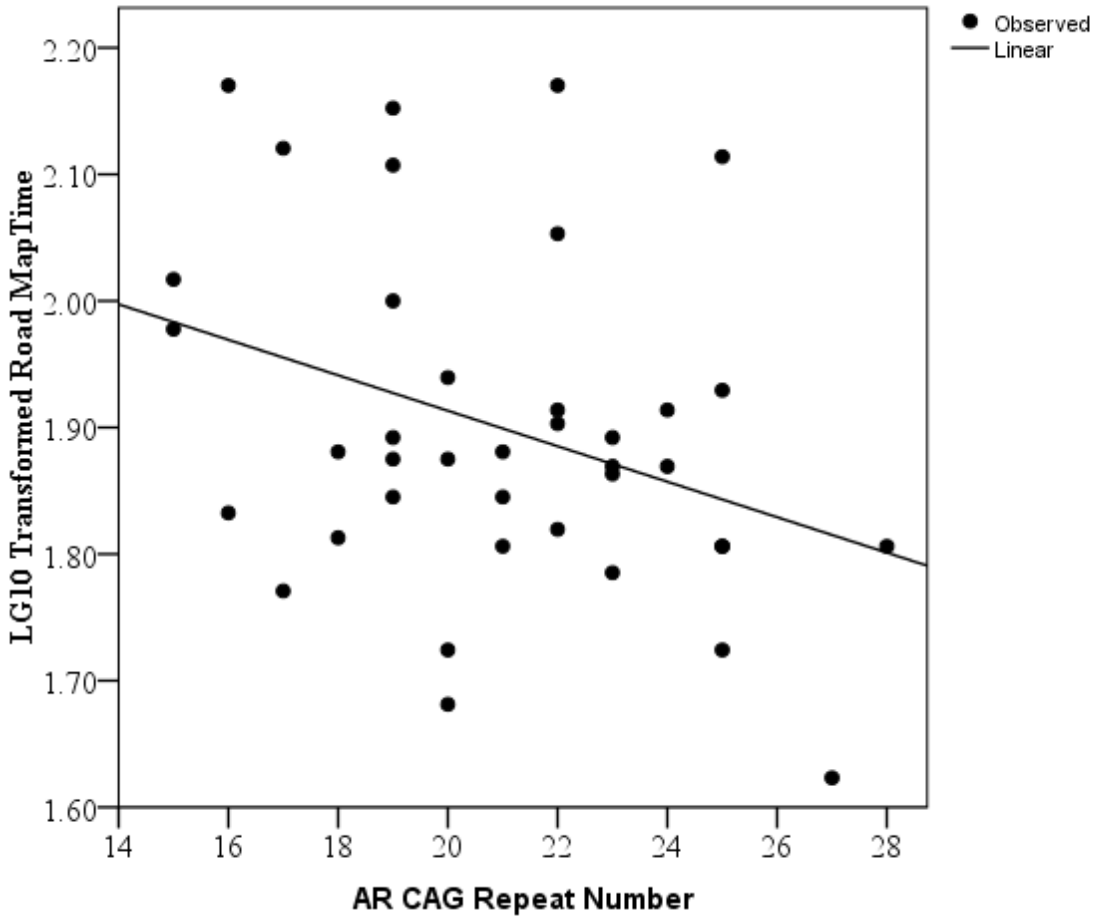


Figure 14. A negative linear correlation between CAGr and time to complete the Money Road Map was observed in women.

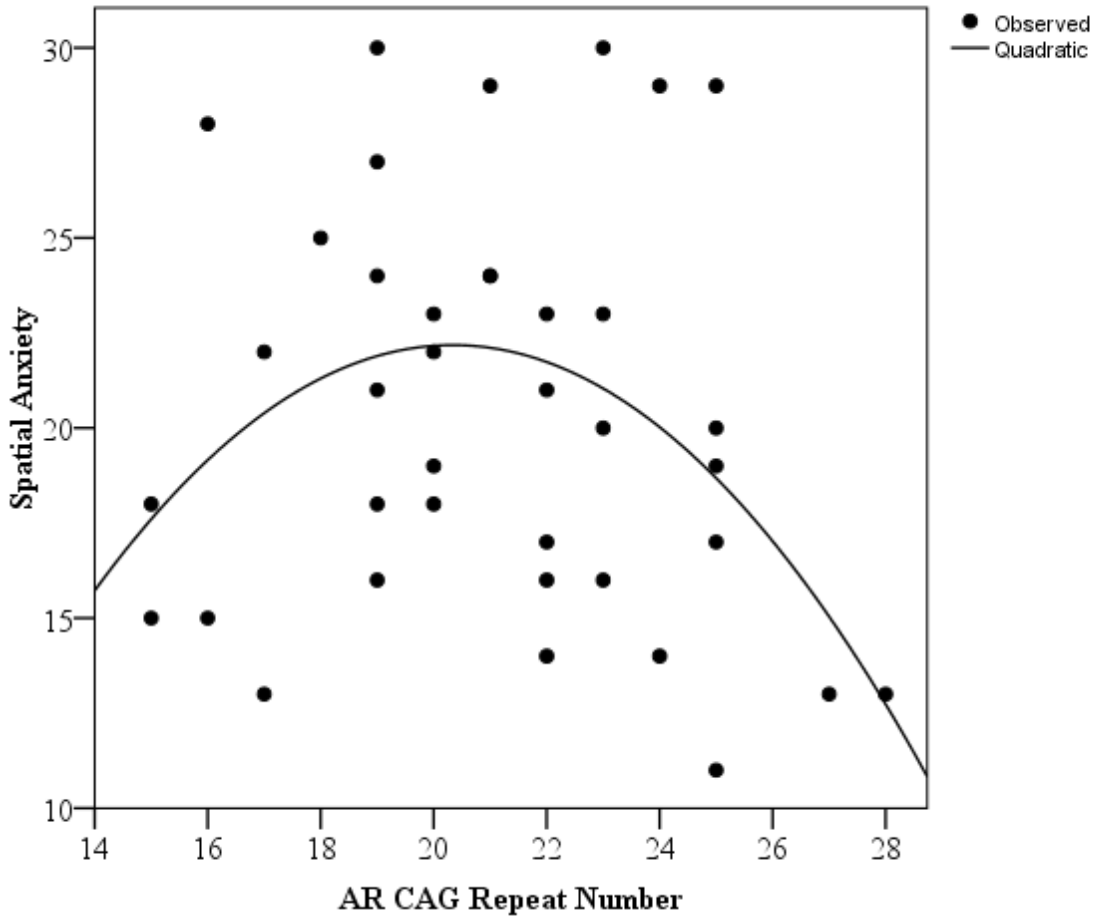


Figure 15. A quadratic relationship was found between CAGr and Spatial Anxiety scores in women.

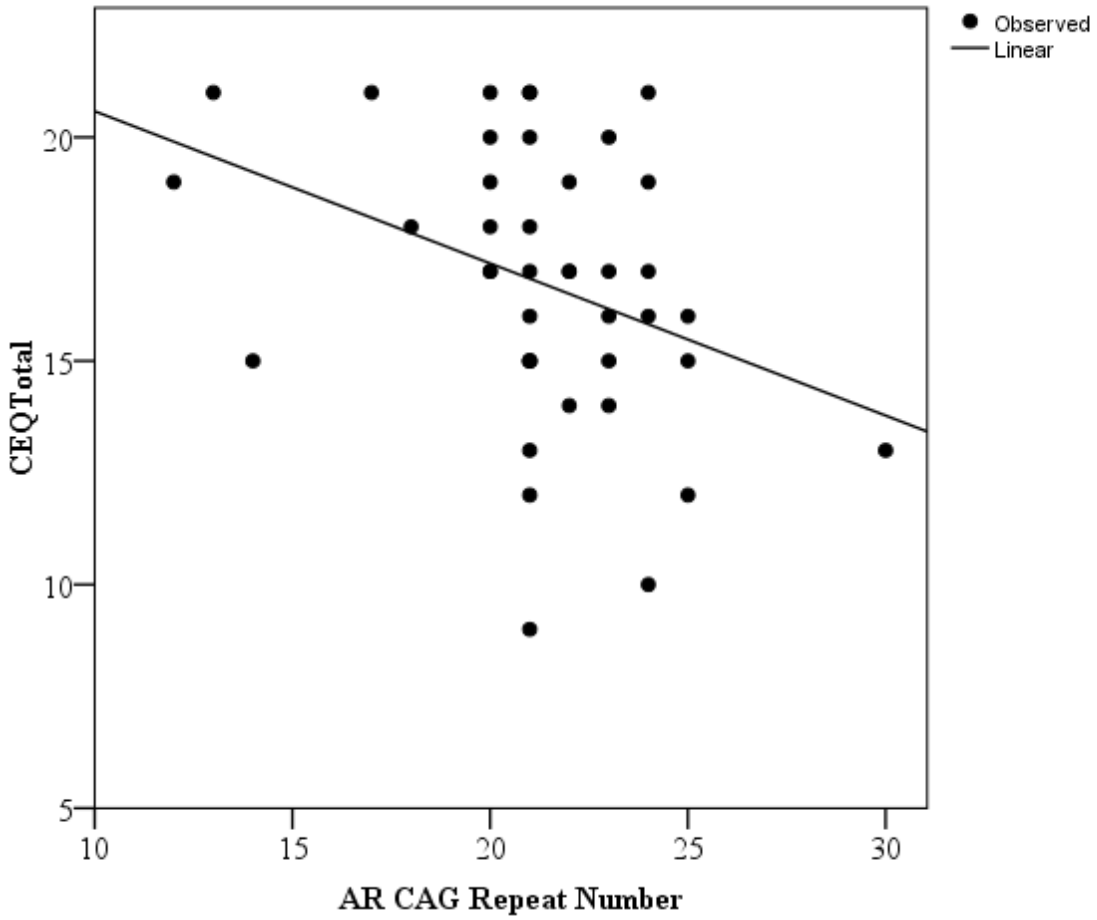


Figure 16. A negative linear correlation between CAGr and CEQ Total scores was observed in men.

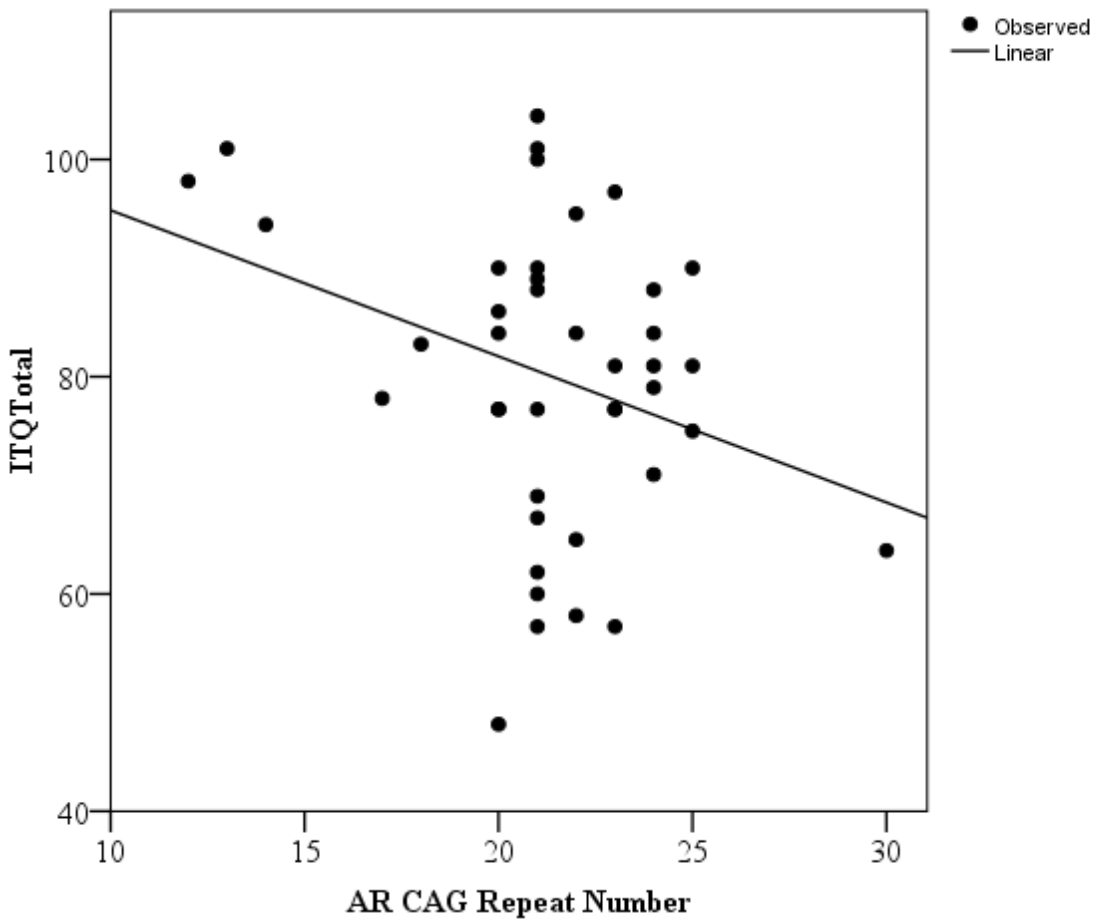


Figure 17. A negative linear correlation was found between CAGr and ITQ Total scores in men.

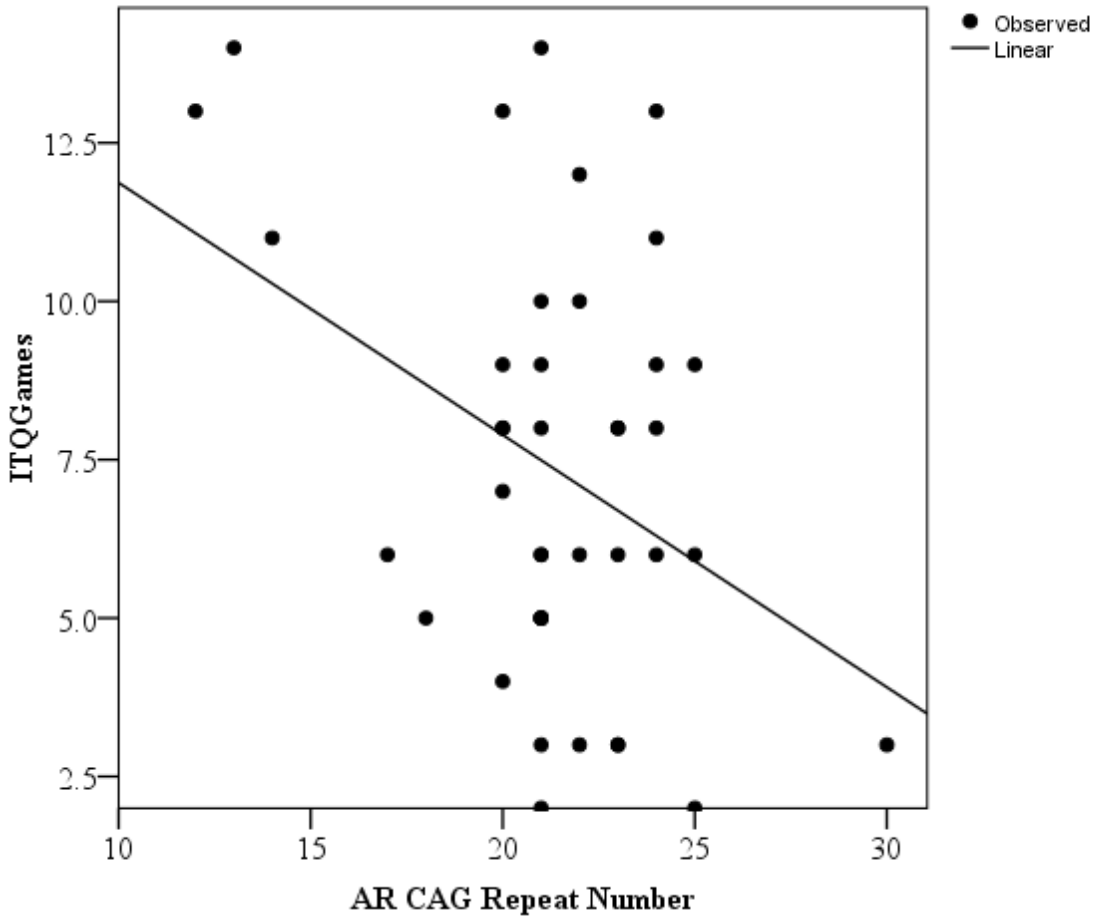


Figure 18. A negative linear correlation between CAGr and ITQ Games scores was found in men.

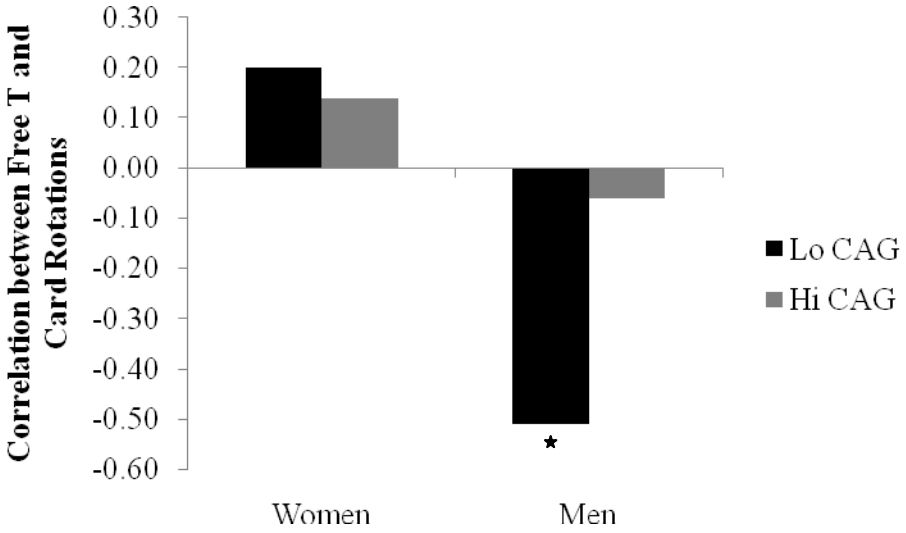


Figure 19. Correlations between free T and Card Rotations (2D mental rotations) scores by sex and CAGr group. The negative linear correlation between T and Card Rotations scores for men in the Lo CAG group was significantly different than zero.

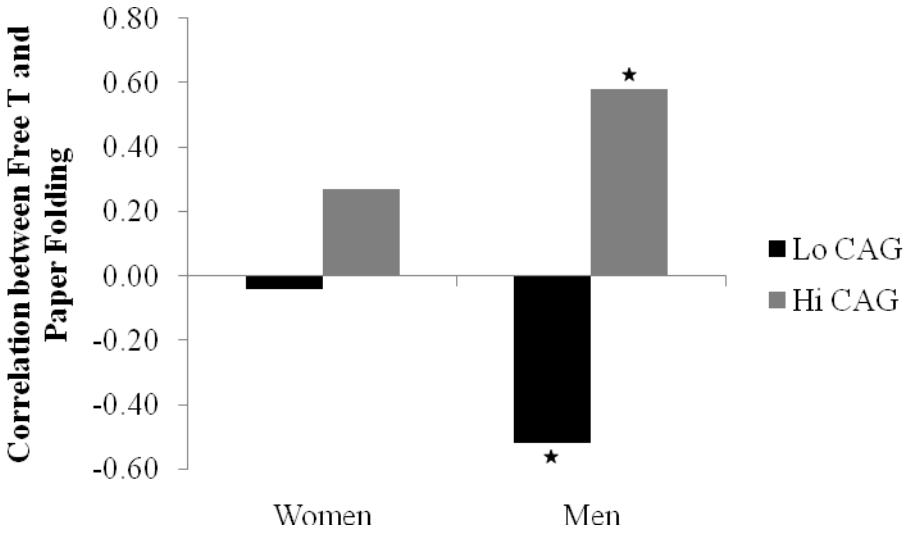


Figure 20. Correlations between free T and Paper Folding scores by sex and CAGr group. The negative and positive correlations between T and Paper Folding scores for men in the two CAG groups were significantly different than zero, and significantly different from each other.

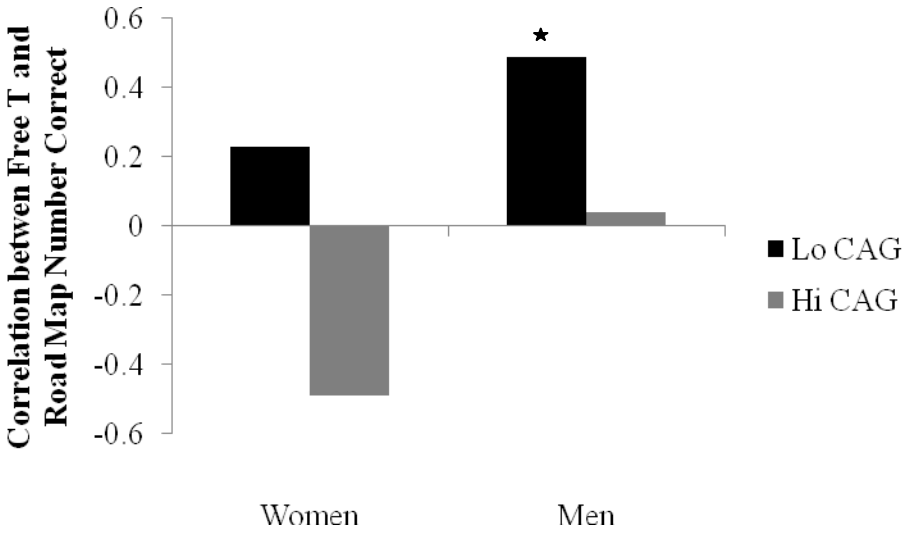


Figure 21. Correlations between free T and number of correct responses on the Money Road Map test by sex and CAGr group. The positive correlation between T and number of correct responses on the Road Map test for men in the Lo CAG group was significantly different than zero.

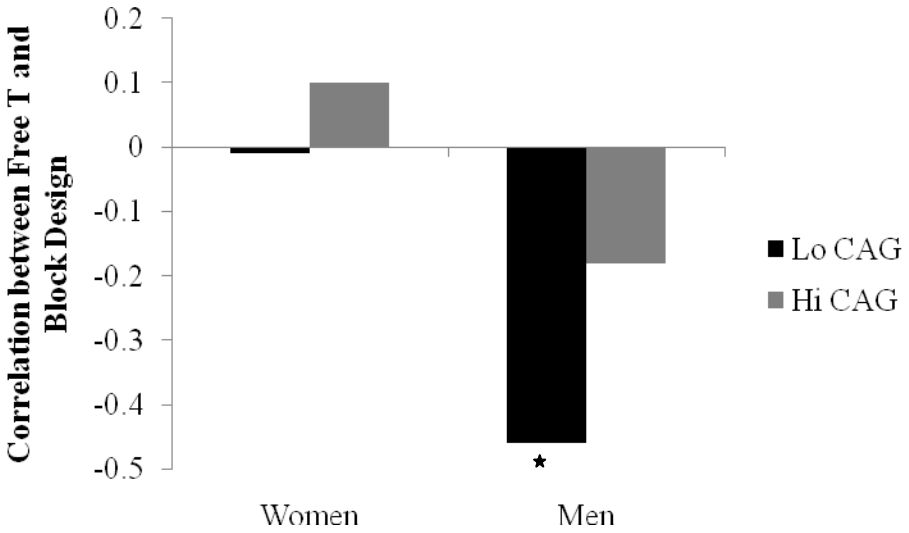


Figure 22. Correlations between free T and Block Design scores by sex and CAGr group. The negative correlation between T and Block Design scores for men in the Lo CAG group was significantly different than zero.

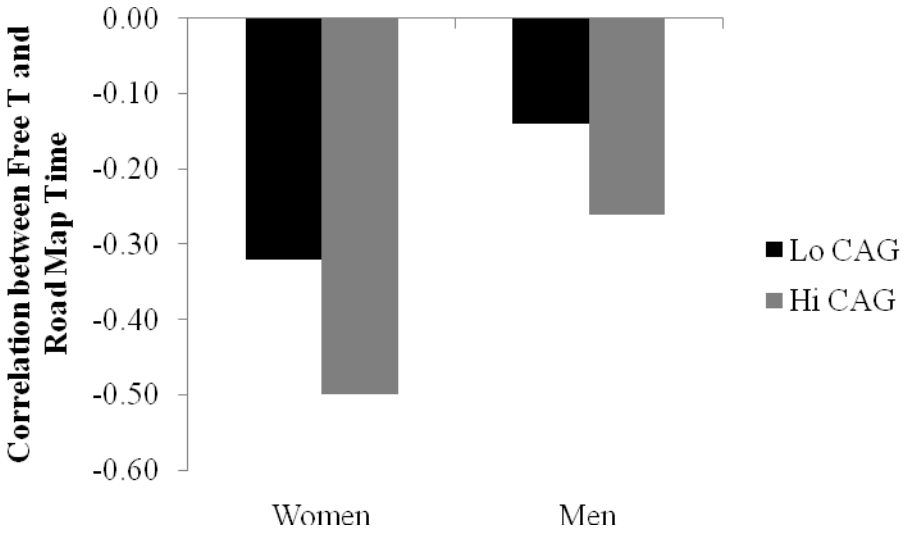


Figure 23. Correlations between free T and time to complete the Money Road Map test by sex and CAGr group.

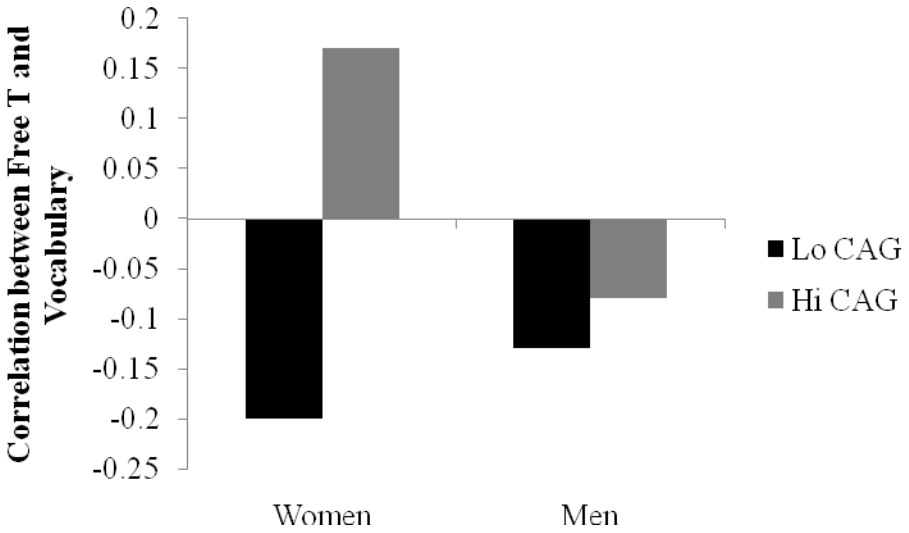


Figure 24. Correlations between free T and Advanced Vocabulary scores by sex and CAGr group.

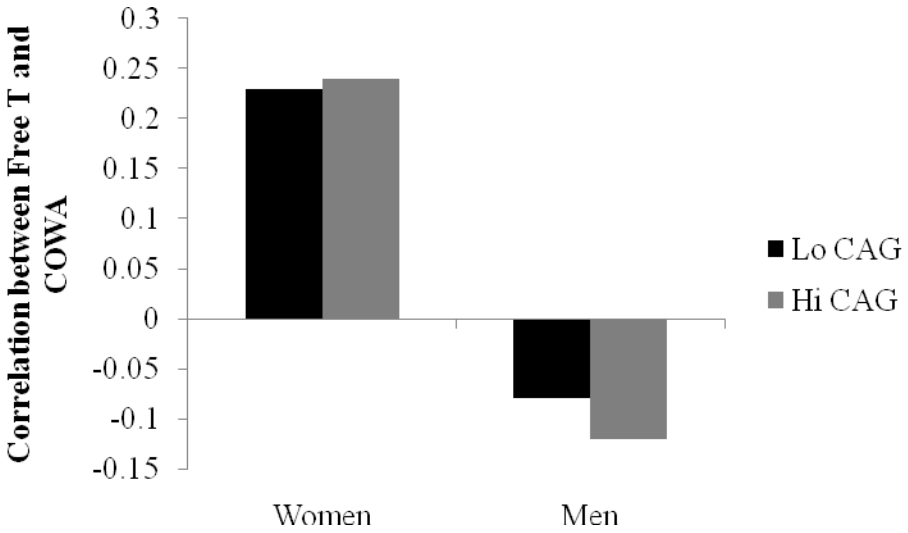


Figure 25. Correlations between free T and COWA (oral word fluency) scores by sex and CAGr group.

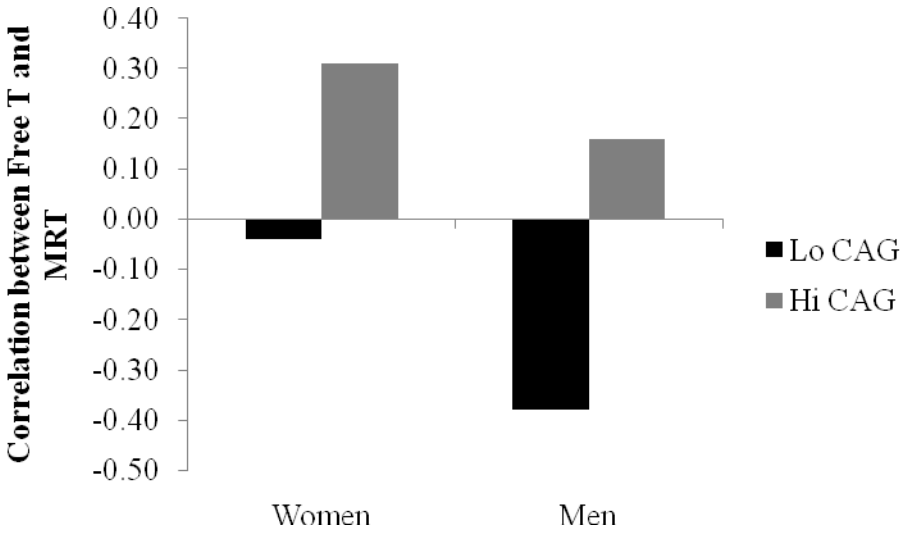


Figure 26. Correlations between free T and MRT (3D mental rotations) scores by sex and CAGr group.

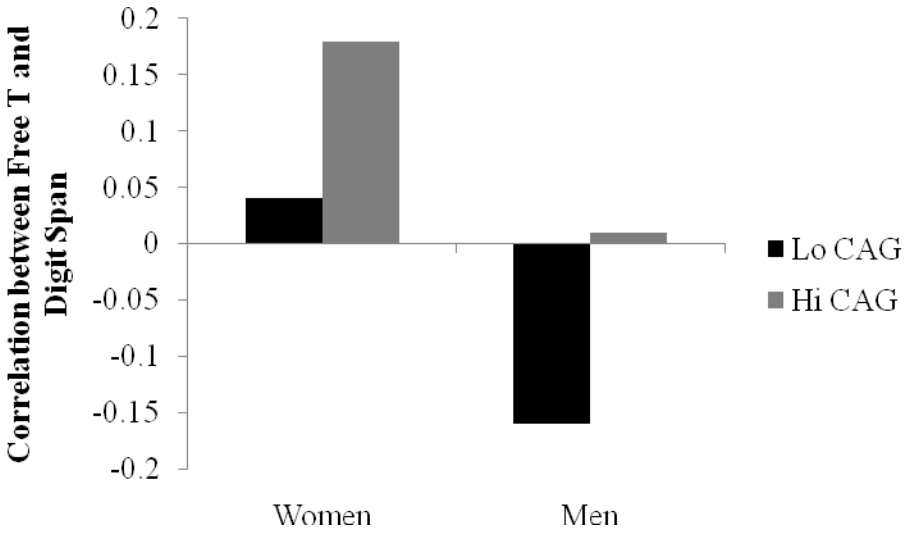


Figure 27. Correlations between free T and Digit Span scores by sex and CAGr group.

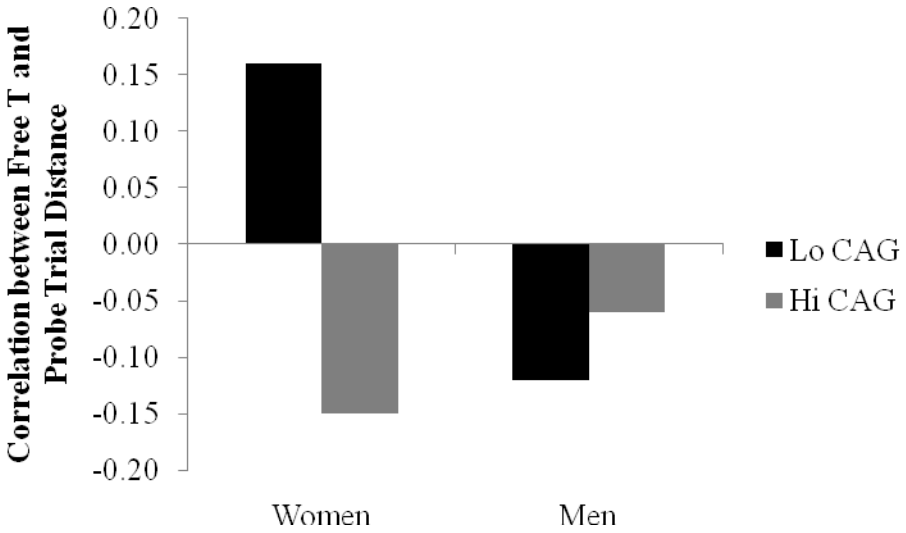


Figure 28. Correlations between free T and total distance traveled in the vMWT probe trial by sex and CAGr group.

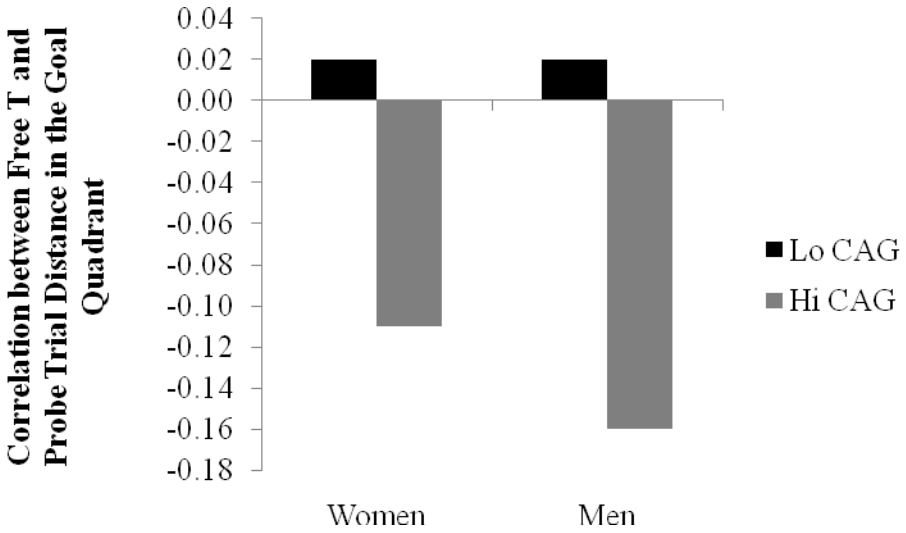


Figure 29. Correlations between free T and distance traveled in the goal quadrant of the vMWT probe trial by sex and CAGr group.

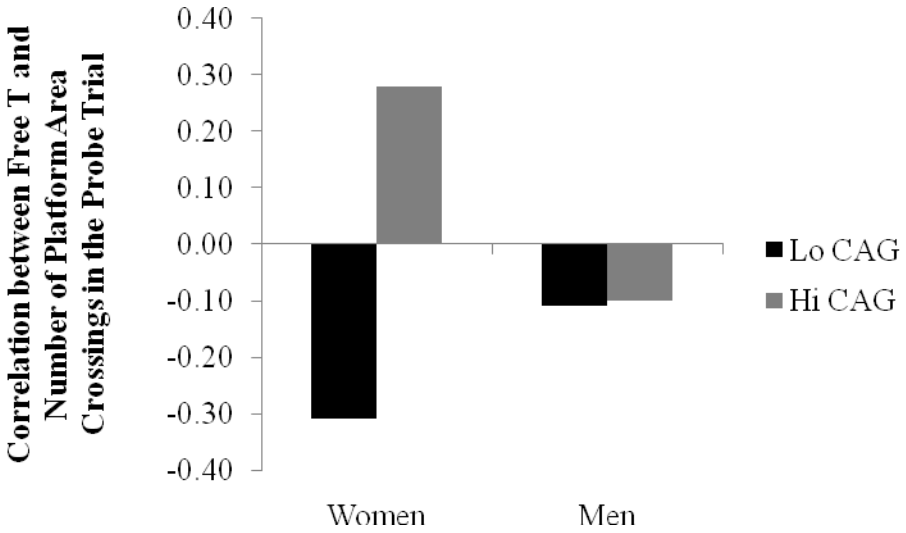


Figure 30. Correlations between free T and number of platform area crossings in the vMWT probe trial by sex and CAGr group.

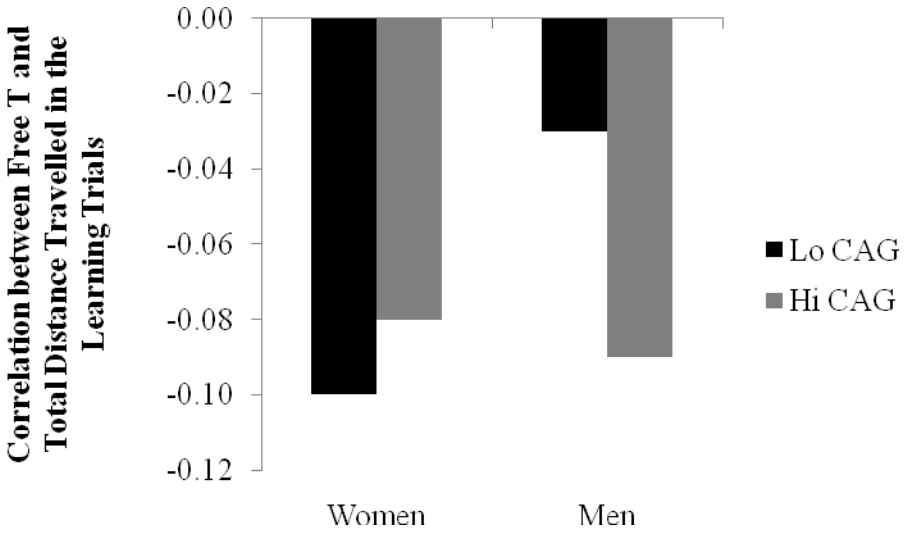


Figure 31. Correlations between free T and total distance traveled in the vMWT learning trials by sex and CAGr group.

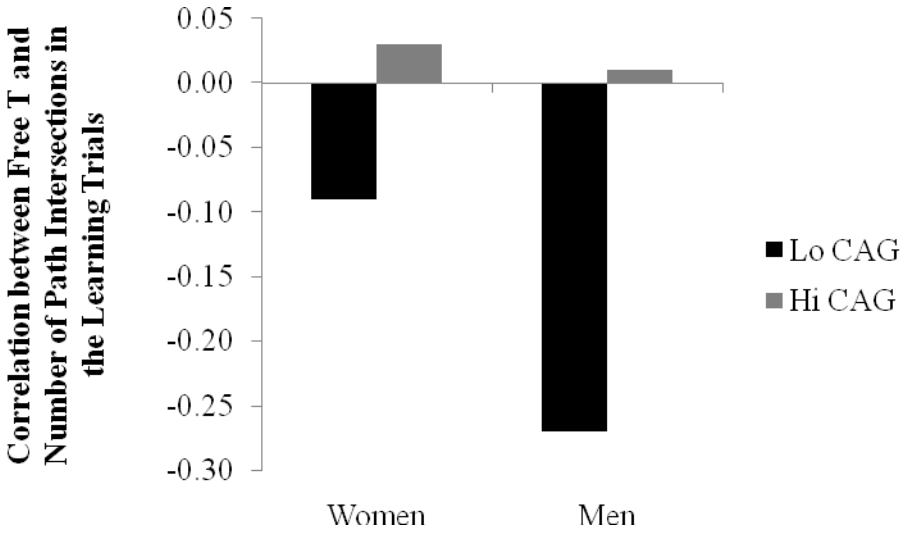


Figure 32. Correlations between free T and number of path intersections across the vMWT learning trials by sex and CAGr group.

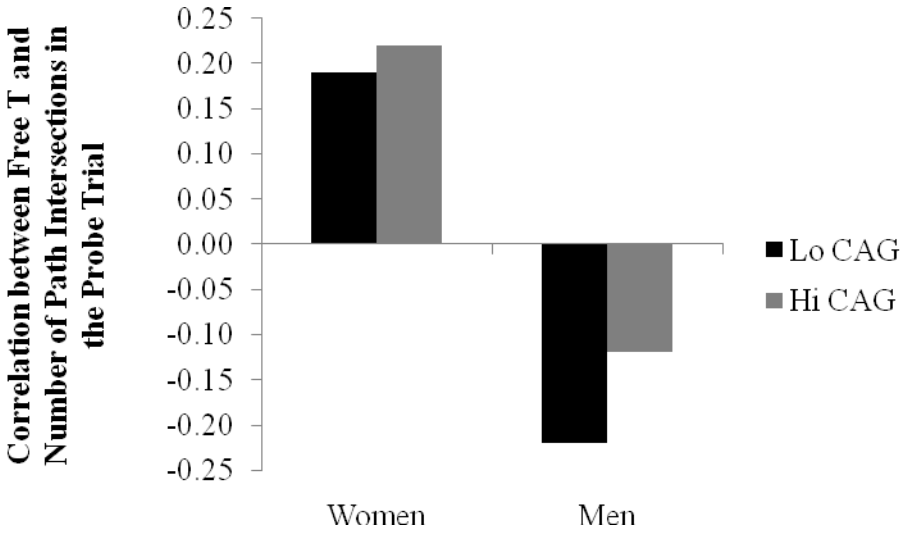


Figure 33. Correlations between free T and number of path intersections in the vMWT probe trial by sex and CAGr group.

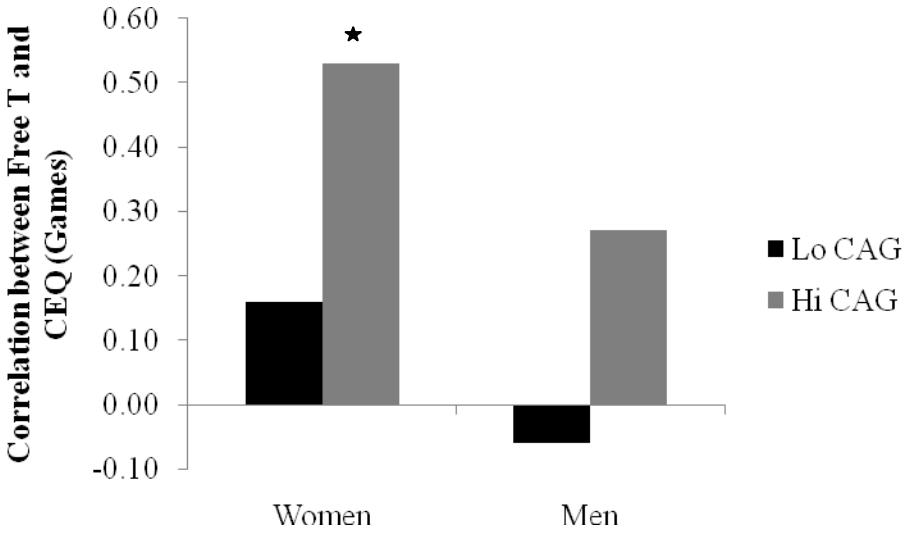


Figure 34. Correlations between free T and video game experience by sex and CAGr group. The postive correlation between T and video game experience for women in the Hi CAG group was significantly different than zero.

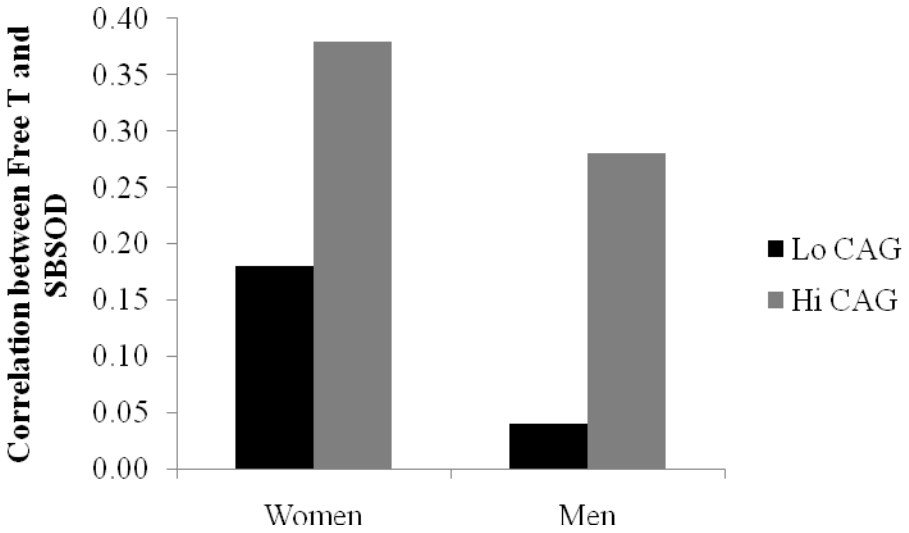


Figure 35. Correlations between free T and SBSOD scores by sex and CAGr group.

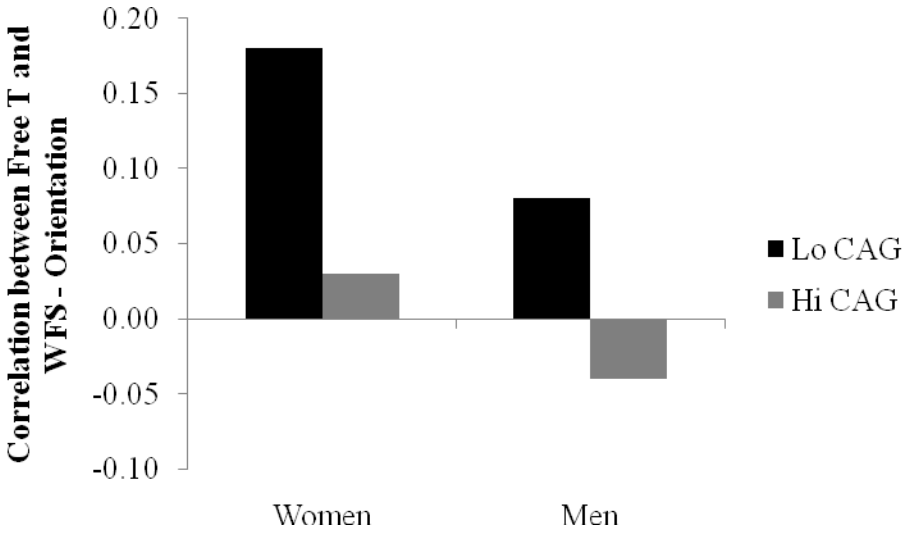


Figure 36. Correlations between free T and orientation-based wayfinding strategy by sex and CAGr group.

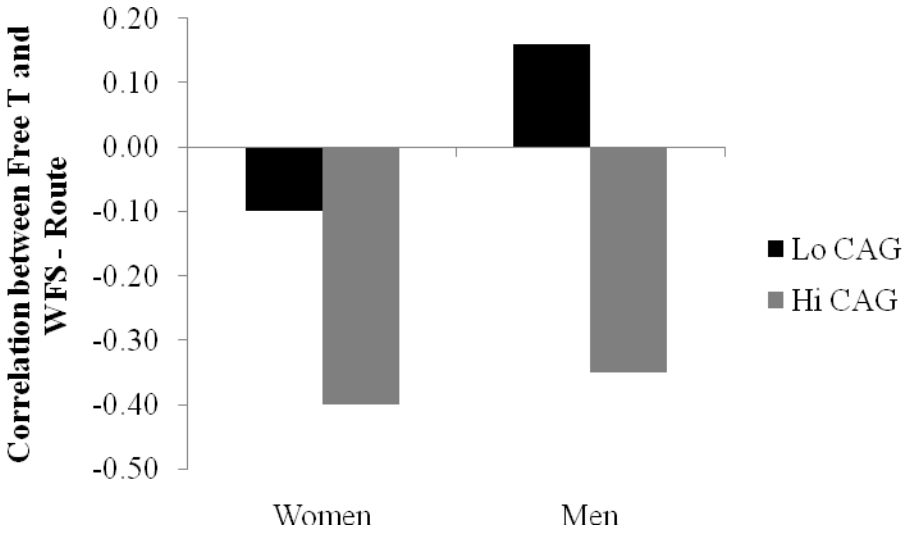


Figure 37. Correlations between free T and route-based wayfinding strategy by sex and CAGr group.

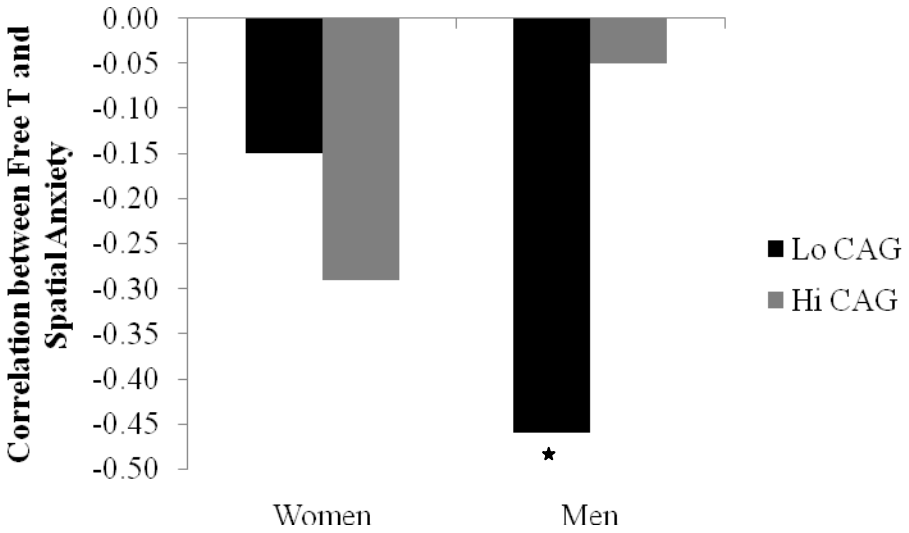


Figure 38. Correlations between free T and Spatial Anxiety scores by sex and CAGr group. The negative correlation between T and Spatial Anxiety scores for men in the Lo CAG group was significantly different than zero.

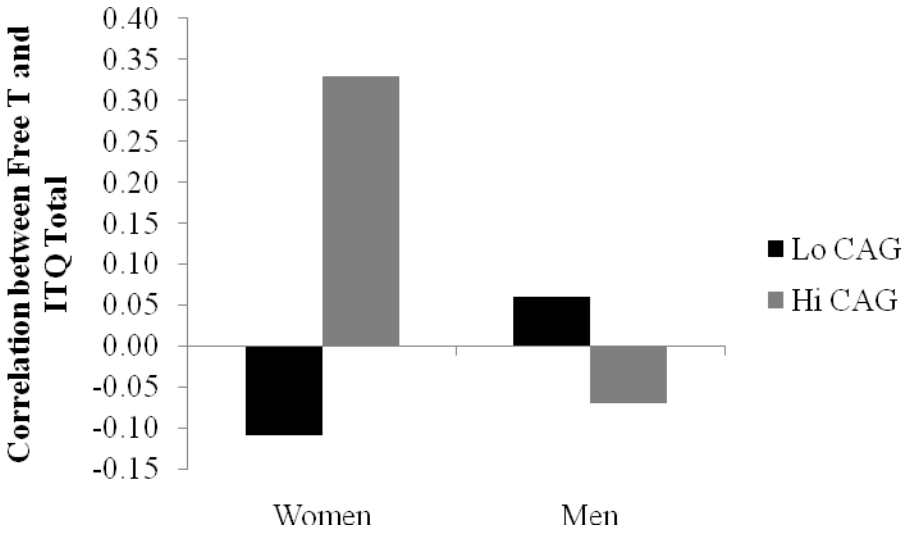


Figure 39. Correlations between free T ITQ scores (subjective sense of being immersed in activities such as video games) by sex and CAGr group.

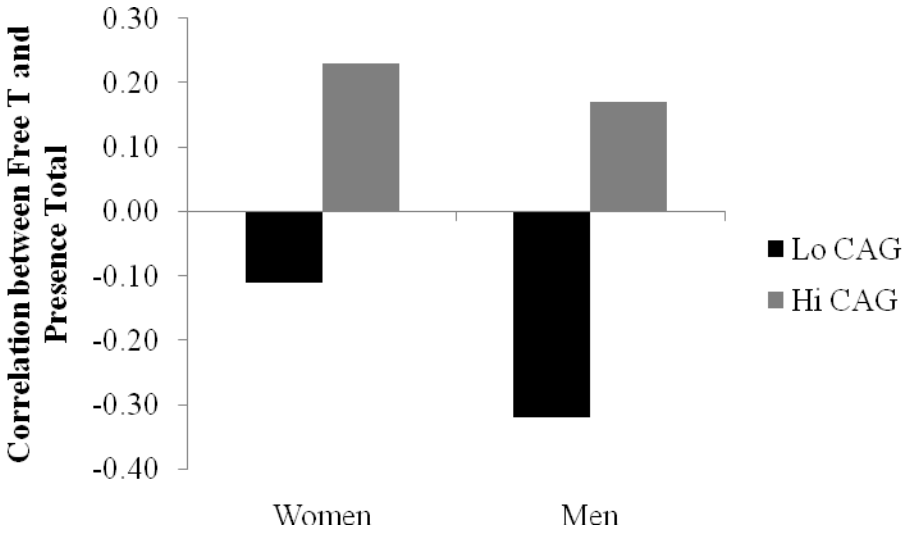


Figure 40. Correlations between free T Presence scores (subjective sense of being present during performance of the vMWT trials) by sex and CAGr group.

APPENDIX C – ABBREVIATION INDEX

2D	two dimensional
3D	three dimensional
AIS	androgen insensitivity syndrome
AR	androgen receptor
BOLD	blood oxygenation level dependent
CAGr	AR CAG repeat number
CAH	congenital adrenal hyperplasia
DG-GCL	dentate gyrus – granule cell layer
DHEA	dehydroepiandrosterone
DHEAS	dehydroepiandrosterone sulfate
DHT	dihydrotestosterone
DHTP	dihydrotestosterone propionate
DNA	deoxyribonucleic acid
ELISA	enzyme-linked immunosorbent assay
F	females (tables only)
fMRI	functional magnetic resonance imaging
FTI	free testosterone index [(T/SHBG) x 100]
GZSO	Guilford-Zimmerman Spatial Orientation test
IHH	idiopathic hypogonadotropic hypogonadism
LIA	chemiluminescence immunoassay
M	males (tables only)

mg	milligrams
MPFB	Minnesota Paper Form Board
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MRT	Mental Rotation Test
ng/dl	nanograms per deciliter
ng/ml	nanograms per milliliter
N/n	Number of subjects/participants in a study (N) or group (n)
OLT	optimal level theory
PCOS	polycystic ovarian syndrome
pg/ml	picograms per milliliter
RIA	radioimmunoassay
SIBT	Stafford Identical Blocks Test
Sry	sex determining region of the Y chromosome
T	testosterone
TP	testosterone propionate
vMWT	virtual Morris water task
VSWM	visuospatial working memory
WAIS	Wechsler Adult Intelligence Scale
WSU	Wayne State University
XX	normal female karyotype
XY	normal male karyotype

REFERENCES

Abdelgadir, S.E., Roselli, C.E., Choate, J.V., & Resko, J.A. (1999). AR messenger ribonucleic acid in brains and pituitaries of male rhesus monkeys: Studies on distribution, hormonal control, and relationship between luteinizing hormone secretion. *Biology of Reproduction, 60(5),* 1251-1256.

Aleman, A., Bronk, E., Kessels, R.P.C., Koppeschaar, H.P.F., & van Honk, J. (2004). A single administration of testosterone improves visuospatial ability in young women. *Psychoneuroendocrinology, 29,* 612-617.

Arnold, A.P. (2004). Sex chromosomes and brain gender. *Nature Neuroscience Review, 5,* 701-708.

Arnold, A.P. & Breedlove, S.M. (1985). Organizational and activational effects of sex steroids on brain and behavior: A reanalysis. *Hormones and Behavior, 19,* 469-498.

Astur, R.S., Ortiz, M.L., & Sutherland, R.J. (1998). A characterization of performance by men and women in a virtual Morris Water task: A large and reliable sex difference. *Behavioral Brain Research, 93,* 185-190.

Astur, R.S., Taylor, L.B., Mamelak, A.N., Philpott, L., & Sutherland, R.J. (2002). Humans with hippocampus damage display severe spatial memory impairments in a virtual Morris water task. *Behavioural Brain Research, 132,* 77-84.

Astur, R.S., Tropp, J., Sava, S., Constable, R.T., & Markus, E. (2004). Sex differences

and correlations in a virtual Morris water task, a virtual radial arm maze, and mental rotation. *Behavioural Brain Research, 151,* 103-115.

Bardin, C.W., Swerdloff, R.S., & Santen, R.J. (1991). Androgens: risks and benefits. *Journal of Clinical Endocrinology and Metabolism, 73(1),* 4-7.

Barnard, L., Balen, A.H., Ferriday, D., Tiplady, B., & Dye, L. (2007). Cognitive functioning in polycystic ovary syndrome. *Psychoneuroendocrinology, 32,* 906-914.

Barrash, J. (1998). A historical review of topographical disorientation and its neuroanatomical correlates. *Journal of Clinical and Experimental Neuropsychology, 20,* 807-827.

Barrash, J., Damasio, H., Adolphs, R., & Tranel, D. (2000). The neuroanatomical correlates of route learning impairment. *Neuropsychologia, 38,* 820-836.

Beatty, W.W. (1984). Hormonal organization of sex differences in play fighting and spatial behavior. *Progress in Brain Research, 61,* 315-330.

Beauchet, O. (2006). Testosterone and cognitive function: current clinical evidence of a relationship. *European Journal of Endocrinology, 155,* 773-781.

Becker, J.B., Breedlove, S.M., Crews, D., & McCarthy, M.M. (2002). *Behavioral Endocrinology.* Cambridge: The MIT Press.

Benton, A. L., & Hamsher, K.(1976). *Multilingual aphasia examination*. Iowa City, IA: AJA.

Beyenburg, S., Watzka, M., Clusmann, H., Blümcke, I., Bidlingmaier, F., Elger, C.E. et al. (2000). Adrogen receptor mRNA expression in the human hippocampus. *Neurosceince Letters, 294,* 25-28.

Bingham, V.P., Ioalé, P., Casini, G., & Bagnoli, P. (1990). The avian hippocampus: Evidence for a role in the development of the homing pigeon navigational map. *Behavioral Neuroscience, 104(6),* 906-911.

Brown, L.N., Lahar, C.J., & Mosley, J.L. (1998). Age and gender related differences in strategy use for route information: A map present direction giving paradigm. *Environment and Behavior, 30(2),* 123-143.

Brown, R.E. (1994). *Introduction to Neuroendocrinology.* (pp. 19-27). New York: Cambridge University Press.

Brum, I.S., Spritzer, P.M., Paris, F., Maturana, M.A., Audran, F., & Sultan, C. (2005). Association between AR gene CAG repeat polymorphism and plasma testosterone levels in postmenopausal women. *Journal of the Society for Gynecologic Investigation, 12,* 135-141.

Buchsbaum, M.S. & Henkin, R.I. (1980). Perceptual abnormalities in patients with chromatin negative gonadal dysgenesis and hypogonadotropic hypogonadism. *International Journal of Neuroscience, 11,* 201-209.

Burger, H.G., Dudley, E.C., Cui, J., Dennerstein, L., & Hopper, J.L. (2000). A prospective longitudinal study of serum testosterone, dehydroepiandrosterone sulface, and sex hormone-binding globulin levels through the menopause transistion. *The Journal of Clinical Endocrinology and Metabolism, 85(8),* 2832-2838.

Burkitt, J., Widman, D., & Saucier, D.M. (2007). Evidence for the influence of testosterone in the performance of spatial navigation in a virtual water maze in women but not in men. *Hormones and Behavior, 51,* 649-654.

Carlson, A.D., Obeid, J.S., Kanellopoulou, N., Wilson, R.C., & New, M.I. (1999). Congenital adrenal hyperplasia: update on prenatal diagnosis and treatment. *The Journal of Steroid Biochemistry and Molecular Biology, 69(1-6),* 19-29.

Carr, B. R., & Rehman, K. S. (2004). Fertilization, Implantation, and Endocrinology of Pregnancy. In J.E. Griffin & S.R. Ojeda (Eds.), *Textbook of Endocrine Physiology* (pp. 249-273). New York: Oxford University Press.

Chamberlain, N.L., Driver, E.D. & Miesfeld, R.L. (1994). The length and location of CAG trinucleotide repeats in the AR N-terminal domain affect transactivation function. *Nucleic Acids Research, 22(15),* 3181-3186.

Cherrier, M.M., Asthana, S., Plymate, S., Baker, L., Matsumoto, A.M., Peskind, E. et al. (2001). Testosterone supplementation improves spatial and verbal memory in healthy older men. *Neurology, 57(1),* 80-88.

Cherrier, M.M., Craft, S., & Matsumoto, A.H. (2003). Cognitive changes associated with supplementation of testosterone or dihydrotestosterone in mildly hypogonadal men: A preliminary report. *Journal of Andrology, 24(4),* 568-576.

Cherrier, M.M., Matsumoto, A.H., Amory, J.K., Ahmed, S., Bremmer, W., Peskind, E.R. et al. (2005). The role of aromatization in testosterone supplementation. *Neurology, 64,* 290-296.

Cherrier, M.M., Rose, A.L., & Higano, C. (2003). The effects of combined androgen blockade on cognitive function during the first cycle of intermittent androgen suppression in patients with prostate cancer. *Journal of Urology, 170(5),* 1808-1811.

Choate, J.V., Slayden, O.D., & Resko, J.A. (1998). Immunocytochemical localization

of ARs in brains of developing and adult male rhesus monkeys. *Endocrine, 8(1),* 51-60.

Choi, J. & Silverman, I. (1997). Sexual dimorphisms in spatial behavior: Applications to route learning. *Evolution and Cognition, 2,* 165-171.

Choi, J. & Silverman, I. (2002). The relationship between testosterone and route-learning strategies in humans. *Brain and Cognition, 50,* 116-120.

Choong, C.S., Kemppainen, J.A., Zhou, Z.X., & Wilson, E.M. (1996). Reduced AR gene expression with first exon CAG repeat expansion. *Molecular Endocrinology, 10,* 1527-1535.

Christiansen, K. & Knussmen, R. (1987). Sex hormones and cognitive functioning in men. *Neuropsychobiology, 18,* 27-36.

Clemens, L., Gladue, B., & Coniglio, L. (1978). Prenatal endogenous androgenic influences on masculine sexual behavior and genital morphology in male and female rats. *Hormones and Behavior, 10,* 40-53.

Clos, V., Esteve, A., Jane, F., Salva, P. (1988). Microsomal effects of cyproterone acetate and flutamide in rat testis. *General Pharmacology, 19(3),* 393-397.

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). Hillsdale, NJ: Lawrence Earlbaum Associates.

Cohen, M.S., Kosslyn, S.M., Breiter, H.C., DiGirolamo, G.J., Thompson, W.L., Anderson, A.K. et al. (1996). Changes in cortical activity during mental rotation: A mapping study using functional MRI. *Brain, 119,* 89-100.

Cohen-Bendahan, C.C.C., van de Beek, C., & Berenbaum, S.A. (2005). Prenatal sex hormone effects of child and adult sex-typed behavior: methods and

findings. *Neuroscience and Biobehavioral Reviews, 29,* 353-384.

Colby, C.L., Duhamel, J.R., & Goldberg, M.E. (1995). Multiple parietal representations of space. In Aertsen & Braitenberg, *Brain theory: biological basis and computational theory of vision.* Cambridge:Elsevier.

Cole-Harding, S., Morstad, A., & Wilson, J. (1988). Spatial abilities in members of opposite sex twin pairs. *Behavior Genetics, 18,* 710.

Coluccia, E. & Louse, G. (2004). Gender differences in spatial orientation: A review. *Journal of environmental psychology, 24,* 329-340.

Corballis, M.C. (1997). Mental rotation and the right hemisphere. *Brain and Language, 57(1),* 100-121.

Couzinet, B., Meduri, G., Lecce, M.G., Young, J., Brailly, S. & Loosfelt, H. et al. (2001). The postmenopausal ovary is not a major androgen-producing gland. *The Journal of Clinical Endocrinology and Metabolism, 86(10),* 5060-5066.

Crabbe, P., Bogaert, V., De Bacquer, D., Goemaere, S., Zmierczak, H., & Kaufman, J. M. (2007). Part of the interindividual variation in serum testosterone levels in healthy men relflects differences in androgen sensitivity and feedback set point: Contribution of the androgen receptor polyglutamine tract polymorphism. *The Journal of Clinical Endocrinology and Metabolism, 92(9),* 3604-3610.

Crocker, L. & Alginia, J. (1986). *Introduction to classical and modern test theory.* New York: Harcourt Brace Jovanovich.

D'Hooge, R., & De Deyn, P.P. (2001). Applications of the Morris water maze in the study of learning and memory. *Brain Research Reviews, 36(1),* 60-90.

Dabbs, J.M. (1990). Salivary testosterone measurements: Reliability across hours,

days, and weeks. *Physiology and Behavior, 48,* 83-86.

Dabbs, J.M., Campbell, B.C., Gladue, B.A., Midgley, A.R., Navarro, M.A., Read, G.F. et al. (1995). Reliability of salivary testosterone measurements: A multicenter evaluation. *Clinical Chemistry, 41(11),* 1581-1584.

Dabbs, J.M., Chang, E., Strong, R., & Milun, R. (1998). Spatial ability, navigation strategy, and geographic knowledge among men and women. *Evolution and Human Behavior, 19,* 89-98.

Daniel, J.M., Winsauer, P.J., Moerschbaecher, J.M. (2003). Castration in rats impairs performance during acquisition of a working memory task and exacerbates deficits in working memory produced by scopolamine and mecamylamine. *Psychopharmacology, 170(3),* 294-300.

Davenport, J.W., Hagquist, W.W., & Rankin, G.R. (1970). The symmetrical maze: An automated closed-field test series for rats. *Behavioral Research Methods and Instrumentation, 2(3),* 112-118.

Davis, S.R., Schneider, D., Sarti, M., Rees, M., & Van Lunsen, H. (2002). Androgen levels in normal and oopherectomized women. *Proceedings of the 10th International Congress on the Menopause, Berlin.*

Dawson, J.L., Cheung, Y.M., & Lau, R.T. (1975). Developmental effects of neonatal sex hormones on spatial and activity skils in the white rat. *Biological Psychology, 3,* 213-229.

DeLeo, V. Lanzetta, D., Vanni, A. L., D'Antona, D., & Serveri, F. M. (1991). Low estrogen oral contraceptives and the hypothalamic-pituitary axis. *Contraception, 44,* 155 - 161.

Demers, L.M. (2008). T and estradiol assays: Current and future trends. *Steroids, 73,* 1333-1338.

Dewing, P., Chiang, C.W., Sinchak, K., Sim, H., Fernagut, P.O., Kelly, S. et al. (2006). Direct regulation of adult brain function by the male-specific factor SRY. *Current Biology, 16(4),* 415-420.

Driscoll, I., Hamilton, D.A., Yeo, R.A., Brooks, W.M., & Sutherland, R.J. (2005). Virtual navigation in humans: the impact of age, sex, and hormones on place learning. *Hormones and Behavior, 47,* 326-335.

Driscoll, I., & Resnick, S. M. (2007). Testosterone and cognition in normal aging and Alzheimer's disease: An update. *Current Alzheimer Research, 4,* 33-45.

Eals, M., & Silverman, I. (1994). The hunter-gatherer theory of spatial sex differences: Proximate factors mediating the female advantage in recall of object arrays. *Ethology and Sociobiology, 15,* 95-105.

Eckel, L., Arnold, A.P., Hampson, E., Becker, J.B., Blaustein, J.D., & Herman, J.P. (2008). Research and methodological issues in the study of sex differences and hormone-behavior relations. In J.B. Becker, K.J. Berkley, N. Geary, E. Hampson, J.P. Herman, & E.A. Young (Eds.), *Sex differences in the brain: from genes to behavior.* (pp. 35-61). New York: Oxford University Press.

Edinger, K.L. & Frye, C.A. (2007). Androgens' performance-enhancing effects in the inhibitory avoidance and water maze tasks may involve actions at intracellular ARs in dorsal hippocampus. *Neurobiology of Learning and Memory, 87,* 201-208.

Ekstrom, R. B., French, J. W., & Harman, H. (1976). Manual for kit of factor-referenced cognitive tests. Princeton, NJ: Educational Testing Service.

Ekstrom, A.D., Kahana, M.J., Caplan, J.B., Fields, T.A., Isham, E.A., Newman, E.L., & Fried, I. (2003). Cellular networks underlying human spatial navigation. *Nature, 425,* 184-187.

Epstein, R. & Kanwisher, N. (1998). A cortical representation of the local visual environment. *Nature, 392(6676),* 598-601.

Feldman, H.A., Longcope, C., Derby, C.A., Johannes, C.B., Araujo, A.B., Coviello, A.D. et al. (2002). Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts male aging study. *Journal of Clinical Endocrinology and Metabolism, 87(2),* 589-598.

Fernández-Guasti, A., Kruijver, F.P., Fodor, M., & Swaab, D.F. (2000). Sex differences in the distribution of ARs in the human hypothalamus. *The Journal of Comparative Neurology, 425(3),* 422-435.

Folstein, M. F., Folstein, S. E., McHugh, P. R. (1975). Mini mental state. A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research, 12(3),* 189-198.

Fonda, S.J., Bertrand, R., O'Donnell, A., Longcope, C., & McKinlay, J.B. (2005). Age, hormones, and cognitive functioning among middle-aged and elderly men: Cross sectional evidence from the Massachusetts male aging study. *Journal of Gerontology, 60(3),* 385-390.

Forger, N.G. (2009). Control of cell number in the sexually dimporphic brain and spinal cord. *Journal of Neuroendocrinology, 21,* 393-399.

Fox, P.T. & Raichle, M.E. (1986). Focal physiological uncoupling of cerebral blood flow and oxidative metabolism during somatosensory stimulation in human subjects. *Proceedings of the National Academy of Sciences, USA, 83,* 1140-1144.

Galea, L.A.M. & Kimura, D. (1993). Sex differences in route learning. *Personality and Individual Differences, 14(1),* 53-65.

Garden, S., Cornoldi, C. & Logie, R.H. (2002). Visuo-spatial working memory in navigation. *Applied Cognitive Psychology, 16(1),* 35-50.

Gardner, D.G. & Schoback, D. (2004). *Greenspan's Basic and Clinical Endocrinology* (8th ed.). Chicago: McGraw Hill.

Gibbs, R.B. (2005). Testosterone and estradiol produce different effects on cognitive performance in male rats. *Hormones and Behavior, 48,* 268-277.

Gladue, B.A., Beatty, W.W., Larson, J., & Staton, R.D. (1990). Sexual orientation and spatial ability in men and women. *Psychobiology, 18,* 101-108.

Gobinet, J., Poujol, N. & Sultan, Ch. (2002). Molecular action of androgens. *Molecular and Cellular Endocrinology, 198,* 15-24.

Gouchie, C. & Kimura, D. (1991). The relationship between testosterone levels and cognitive ability patterns. *Psychoneuroendocrinology, 16,* 323-324.

Gould, E., Woolley, C.S., Frankfurt, M., & McEwen, B.S. (1990). Gonadal steroids regulate dendritic spine density in hippocampal pyramidal cells in adulthood. *Journal of Neuroscience, 10,* 1286-1291.

Govind, A., Obhrai, M.S., & Clayton, R.N. (1961). Polycystic ovaries are inherited as an autosomal dominant trait. *Journal of Clinical Endocrinology, 21,* 1440.

Goy, R.W. & McEwen, B.S. (1980). *Sexual differentiation of the brain.* Cambridge: MIT Press.

Griffin, J.E. (2004). Male reproductive function. In J.E. Griffin & S.R. Ojeda (Eds.), *Textbook of Endocrine Physiology.* (pp. 226-248). New York: Oxford University Press.

Griffin, J.E. & Auchus, R.J. (2004). Assessment of endocrine function. In J.E. Griffin & S.R. Ojeda (Eds.). *Textbook of Endocrine Physiology.* (pp. 101-119). New York: Oxford University Press.

Griffin, J.E., & Ojeda, S.R. (Eds.) (2004). *Textbook of Endocrine Physiology.* New York: Oxford University Press.

Grimshaw, G.M., Sitarenios, G., & Finegan, J.K. (1995). Mental rotation at 7 years: Relations with prenatal testosterone levels and spatial play experiences. *Brain and Cognition, 29,* 85-100.

Grön, G., Wunderlich, A.P., Spitzer, M., Tomczak, R., & Riepe, M.W. (2000). Brain activation during human navigation: gender-different neural networks as substrate of performance. *Nature Neuroscience, 3(4),* 404-408.

Grumbach, M.M. & Conte, F.A. (1992). Disorders of sex differentiation. In J.D. Wilson & D.W. Foster (Eds.), *Williams Textbook of Endocrinology (8th ed.)*. Philadelphia: W.B. Saunders

Grumbach, M.M. & Styne, D.M. (1992). Puberty: ontogeny, neuroendocrinology, physiology and disorders. In J.D. Wilson & D.W. Foster (Eds.), *Williams Textbook of Endocrinology (8th ed.)*. Philadelphia: W.B. Saunders.

Gur, R.C., Turetsky, B.I., Matsui, M., Yan, M., Bilker, W., Hughett, P. et al. (1999). Sex differences in brain gray and white matter in healthy young adults: correlations with cognitive performance. *The Journal of Neuroscience, 19(10),* 4065-4072.

Halari, R., Sharma, T., Hines, M., Andrew, C., Simmons, A., & Kumari, V. (2006). comparable fMRI activity with differential behavioural performance on mental rotation and overt verbal fluency tasks in healthy men and women. *Experimental Brain Research, 169,* 1-14.

Hampson, E., & Kimura, D. (1988). Reciprocal effects of hormonal fluctuations on human motor and perceptual-spatial skills. *Behavioral Neuroscience, 102(3),* 456-459.

Hampson, E. & Kimura, D. (1992). Sex differences and hormonal influences on cognitive function in humans. In J.B. Becker, S.M. Breedlove, & D. Crews (Eds.), *Behavioral Endocrinology,* (pp. 357-398). Cambridge, MA: MIT Press.

Hampson, E., Rovet, J.F., & Altman, D. (1998). Spatial reasoning in children with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *Developmental Psychology, 14,* 299-320.

Hampson, E. & Young, E.A. (2008). Methodological issues in the study of hormone-behavior relations in humans: Understanding and monitoring the menstrual cycle. In J.B. Becker, K.J. Berkley, N. Geary, E. Hampson, J.P. Herman, & E.A. Young (Eds.), *Sex differences in the brain: from genes to behavior.* (pp. 63-78). New York: Oxford University Press.

Harooni, H.E., Naghdi, N., Sepehri, H., & Rohani, A.H. (2008). Intrahippocampal injection of testosterone impaired acquisition, consolidation and retrieval of inhibitory avoidance learning and memory in adult male rats. *Behavioural Brain Research, 188(1),* 71-77.

Hasegawa, N. & Mochizuki, M. (2009). Improved effect of Pycnogenol® on impaired spatial memory function in partial androgen deficiency in rat model. *Phytotherapy Research, 23,* 840-843.

Hassler, M., Gupta, D., & Wollmann, H. (1992). Testosterone, estradiol, ACTH, and musical, spatial and verbal performance. *International Journal of Neuroscience, 65,* 45-60.

Hausmann, M., Schoofs, D., Rosenthal, H.E., & Jordan, K. (2009). Interactive effects of sex hormones and gender stereotypes on cognitive sex differences: A psychobiosocial approach. *Psychoneuroendocrinology, 34(3),* 389-401.

Head, D. P. I. (2001). *The role of executive functions in age differences in episodic memory.* Retrieved from UMI (3029893).

Hegarty, M., Richardson, A. E., Montello, D. R., Lovelace, K., Subbiah, I. (2002). Development of a self-report measure of environmental spatial ability. *Intelligence, 30,* 425-447.

Hier, D.B., & Crowley, W.F., Jr. (1982). Spatial ability in androgen-deficient men. *The New England Journal of Medicine, 306(20),* 1202-1205.

Hietala, M., Sandberg, T., Borg, Å, Olsson, H., & Jernström, H. (2007). T levels in relation to oral contraceptive use and the AR CAG and GGC length polymorphisms in healthy young women. *Human Reproduction, 22*

(1), 83-91.

Hines, M. (2004). *Brain Gender.* New York: Oxford University Press.

Hines, M., Ahmed, S.F., & Hughes, I.A. (2003). Psychological outcomes and gender-related development in complete androgen insensitivity syndrome. *Archives of Sexual Behavior, 32(2),* 93-101.

Hines, M., Fane, B.A., Pasterski, V.L., Matthews, G.A., Conway, G.S., & Brook, C. (2003). Spatial abilities following prenatal androgen abnormality: Targeting and mental rotations performance in individuals with congenital adrenal hyperplasia. *Psychoneuroendocrinology, 28(8),* 1010-1026.

Hogervorst, E., Bandelow, S., & Moffat, S.D. (2005). Increasing testosterone levels and effects on cognitive functions in elderly men and women: a review. *Current Drug Targets CNS Neurological Disorders, 4,* 531-540.

Holland, J., Bandelow, S., & Hogervorst, E. (2011). Testosterone levels and cognition in elderly men: A review. *Maturitas, 69(4),* 322-337.

Hooven, C.K., Chabris, C.F., Ellison, P.T., Kosslyn, S.M. (2004). The relationship of male testosterone to components of mental rotation. *Neuropsychologia, 42,* 782-790.

Hsing, A. W., Stanczyk, F. Z., Bélanger, A., Schroeder, P., Chang, L., Falk, R. T. et al. (2007). Reproducibility of serum sex steroid assays in men by RIA and mass spectrometry. *Cancer Epidemiology, Biomarkers & Prevention, 16(5),* 1004-8.

Hugdahl, K., Thomsen, T., & Ersland, L. (2006). Sex differences in visuo-spatial processing: An fMRI study of mental rotation. *Neuropsychologia, 44,* 1575-

1583.

Hughes, I.A. (2001). Minireview: sex differentiation. *Endocrinology, 142,* 3281-3287.

Huntaniemi, I.T., Pye, S.R., Limer, K.L., Thomson, W., O'Neill, T.W., Platt, H. et al. (2009). Increased estrogen rather than decreased androgen action is associated with longer androgen receptor CAG repeats.

Hyde, J.S. (1981). How large are cognitive gender differences? *American Psychologist, 36,* 892-901.

Iaria, G., Petrides, M., Dagher, A., Pike, B., & Bohbot, V.D. (2003). Cognitive strategies dependent of the hippocampus and caudate nucleus in human navigation: Variability and change with practice. *The Journal of Neuroscience, 23(13),* 5945- 5952.

Ibáñez, L., Ong, K.K., Mongan, N., Jaaskelainen, J., Marcos, M.V., Hughes, I.A. et al. (2008). Androgen receptor gene CAG repeat polymorphism in the development of ovarian hyperandrogenism. *The Journal of Clinical Endocrinology and Metabolism, 88(7),* 3333-3338.

Imperato-McGinley, J., Peterson, R.E., Gautier, T., Cooper, G., Danner, R., Arthur A. et al. (1982). Hormonal evaluation of a large kindred with complete androgen insensitivity: evidence for secondary 5 alpha-reductase deficiency. *Journal of Clinical Endocrinology and Metabolism, 54(5),* 931-941.

Imperato-McGinley, J., Pichardo, M., Gautier, T., Voyer, D., & Bryden, P. (1991). Cognitive abilities in androgen-insensitive subjects: comparison with control males and females from the same kindred. *Clinical Endocrinology, 34,* 341-347.

Isgor, C., & Sengelaub, D.R. (1998). Prenatal gonadal steroids affect adult spatial

behavior, CA1 and CA3 pyramidal cell morphology in rats. *Hormones and Behavior, 34(2),* 183-198.

Isgor, C., & Sengelaub, D.R. (2003). Effects of neonatal gonadal steroids on adult CA3 pyramidal neuron dendritic morphology and spatial memory in rats. *Journal of Neurobiology, 55(2),* 179-190.

Jaaskelainen, J., Korhonen,, S., Voutilainen, R., Hippelainen, M, & Heinonen, S. (2005). AR gene CAG length polymorphism in women with polycystic ovary syndrome. *Fertility and Sterility, 83,* 1724-1728.

Jacobson, C.D. & Gorski, R.A. (1981). Neurogenesis of the sexually dimporphic nucleus of the preoptic area of the rat. *Journal of Comparative Neurology, 196,* 519-529.

Jaeger, J.J., Lockwood, A.H., Van Valin, R.D., Kemmerer, D.L., Murphy, B.W., & Wack, D.S. (1998). Sex differences in brain regions activated by grammatical and reading tasks. *Neuroreport, 9(12),* 2803-2807.

Jamison, C.S., Meier, R.J., & Campbell, B.C. (1993). Dermatoglyphic asymmetry and tesosterone levels in normal males. *American Journal of Physical Anthropology, 90,* 185-198.

Janowsky, J.S., Oviatt, S.K., Orwoll, E.S. (1994). Tesosterone influences spatial cognition in older men. *Behavioral Neuroscience, 108,* 325-332.

Janzen, G., Jansen, C., & van Turennout, M. (2008). Memory consolidation of landmarks in good navigators. *Hippocampus, 18,* 40-47.

Janzen, G. & van Turennout, M. (2004). Selective neural representation of objects relevant for navigation. *Nature Neuroscience, 7,* 673-677.

Jiroutek, M.R., Chen, M.H., Johnston, C.C., & Longcope, C. (1998). Changes in

reproductive hormones and sex hormone-binding globulin in a group of postmenopausal women measured over 10 years. *Menopause, 5(2),* 90-94.

Jonasson, Z. (2005). Meta-analysis of sex differences in rodent models of learning and memory: a review of behavioral and biological data. *Neuroscience and Biobehavioral Reviews, 28,* 811-825.

Jones, B.A. & Watson, N.V. (2005). Spatial memory performance in androgen insensitive male rats. *Physiology and Behavior, 85,* 135-141.

Jordan, K., Wüstenberg, T., Heinze, H.J., Peters, M., & Jäncke, L. (2002). Women and men exhibit different cortical activation patterns during mental rotation tasks. *Neuropsychologia, 40(13),* 2397-2408.

Joseph, R., Hess, S., & Birecree, E. (1978). Effects of hormone manipulations and exploration on sex differences in maze learning. *Behavioral Biology, 24,* 364-377.

Josso, N. (2008). Professor Alfred Jost: the builder of modern sex differentiation. *Sexual Development, 2(2),* 55-63.

Kansaku, K., Yamaura, A., Kitazawa, S. (2000). Sex differences in lateralization revealed in the posterior language areas.. *Cerebral Cortex, 10(9),* 866-872.

Karádi, K., Kállai, J., Kövér, F., Nemes, J., Makány, T., & Nagy, F. (2006). Endogenous T concentration, mental rotation, and size of the corpus callosum in a sample of young Hungarian women. *Perceptual and Motor Skills, 102,* 445-453.

Kaufman, A.S. (1990). *Assessing adolescent and adult intelligence.* Boston: Allyn and Bacon.

Kazemi-Esfarjani, P., Trifiro, M.A., & Pinsky, L. (1995). Evidence for a repressive function of the long polyglutamine tract in the human AR: possible pathogenic relevance for the (CAG)n-expanded neuropathies. *Human Molecular Genetics, 4(4),* 523-527.

Kerr, J.E., Allore, R.J., Beck, S.G., & Handa, R.J. (1995). Distribution and hormonal regulation of AR (AR) and AR messenger ribonucleic acid in the rat hippocampus. *Endocrinology, 136(8),* 3213-3221.

Kesner, R.P., Hunsaker, M.R., & Warthen, M.W. (2008). The CA3 subregion of the hippocampus is critical for episodic memory processing by means of relational encoding in rats. *Behavioral Neuroscience, 122(6),* 1217-1225.

Kessels, R.P., de Haan, E.H., Kappelle, L.J., & Postma, A. Varieties of human spatial memory: a meta-analysis on the effects of hippocampal lesions. *Brain Research Reviews, 35(3),* 295-303.

Kimura, D. (1999). *Sex and Cognition*. The MIT Press: Cambridge, MA.

Kimura, D. & Hampson, E. (1994). Cognitive pattern in men and women is influenced by fluctuation in sex hormones. *Current Directions in Psychological Science, 3(2),* 57-61.

Koscik, T., O'Leary, D., Moser, D.J., Andreasen, N.C., & Nopoulos, P. (2009). Sex differences in parietal lobe morphology: Relationship to mental rotation performance. *Brain and Cognition, 69,* 451-459.

Krithivas, K., Yurgalevitch, S.M., Mohr, B.A., Wilcox, C.J., Batter, S.J., Brown, M. et al. (1999). Evidence that the CAG repeat in the AR gene is associated with the age-related decline in serum androgen levels in men. *Journal*

of Endocrinology, 162, 137-142.

Kritzer, M.F., McLaughlin, P.J., Smirlis, T., Robinson, J.K. (2001). Gonadectomy impairs T-maze acquisition in adult male rats. *Hormones and Behavior, 39(2),* 167-174.

Kwong, K., Belliveau, J., Chesler, D., Goldberg, I., Weisskoff, R., Poncelet, B. et al. (1992). Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. *Proceedings of the National Academy of Sciences, USA, 89,* 5675.

Labrie, F., Belanger, A., Cusan, L., Gomez, J.L., Candas, B. (1997). Marked decline in serum concentrations of adrenal C19 sex steroid precursors and conjugated androgen metabolites during aging. *Journal of Clinical Endocrinology and Metabolism, 82(8),* 2396-2402.

Lamberts, S.W., van den Beld, A.W., & van der Lely, A.J. (1997). The endocrinology of aging. *Science, 278(5337),* 419-424.

Lancaster, J. L., Tordesillas-Guitierrez, D., Martinez, M., Salinas, F., Evans, A., Zilles, K. et al. (2007). Bias between MNI and Talairach coordinates analyzed using the ICBM-152 brain template. *Human Brain Mapping, 28,* 1194-1205.

Lancaster, J. L., Woldorff, M. G., Parsons, L. M., Liotti, M., Freitas, C. S., Rainey, L. et al. (2000). Automated Talairach atlas labels for functional brain mapping. *Human Brain Mapping, 10,* 120-131.

La Spada, A.R., Wilson, E.M., Lubahn, D.B., Harding, A.E., & Fischbeck, K.H. (1991). AR gene mutation in X-linked spinal and bulbar muscular atrophy. *Nature, 352,* 77-79.

Lawton, C. A. (1994). Gender differences in way-finding strategies: relationship to

spatial ability and spatial anxiety. *Sex Roles, 30(11-12),* 765-779.

Lawton, C. A. & Morrin, K. A. (1999). Gender differences in pointing accuracy in computer simulated 3D mazes. *Sex Roles, 40(1-2),* 73-92.

Legro, R. S., Schlaff, W. D., Diamond, M. P., Coutifaris, C., Casson, P. R., Brzyski, R. G. et al. (2010). Total testosterone assays in women with polycystic ovary syndrom: Precision and correlation with hirsutism. *Journal of Clinical Endocrinology and Metabolism, 95(12),* 5305-5313.

Lehman, D.J., Butler, H.T., Warden, D.R., Combrinck, M., King, E., Nicoll, J.A.R. et al. (2003). Association of the AR CAG repeat polymorphism with Alzheimer's disease in men. *Neuroscience Letters, 340,* 87-90.

Leranth, C., MacLusky, N.J., & Hajszan, T. (2008). Sex differences in neuroplasticity. In J.B. Becker, K.J. Berkley, N. Geary, E. Hampson, J.P. Herman, & E.A. Young (Eds.), *Sex differences in the brain: from genes to behavior.* (pp. 201-226). New York: Oxford University Press.

Lim, H.N., Nixon, R.M., Chen, H., Hughes, I.A., Hawkins, J.R. (2001). Evidence that longer AR polyglutamine repeats are a causal factor for genital abnormalities. *Journal of Clinical Endocrinology and Metabolism, 86,* 3207-3210.

Linn, M.C., & Petersen, A.C. (1985). Emergence and characterization of gender differences in spatial abilities: A meta-analysis. *Child Development, 56,* 1479-1498.

Lu, S.F., Mo, Q., Hu, S., Garippa, C., & Simon, N.G. (2003). Dehydroepiandrosterone upregulates neural AR level and transcriptional activity. *Journal of Neurobiology, 57(2),* 163-171.

MacFadden, A., Elias, L., & Saucier, D. (2003). Males and females scan maps similarly but give directions differently. *Brain and Cognition, 53,* 297-300.

Maccoby, E.E., & Jacklin, C.N. (1974). *Psychology of sex differences.* Stanford, CA: Stanford University Press.

MacLusky, N.J. & Naftolin, F. (1981). Sexual differentiation of the central nervous system. *Science, 211,* 1294-1302.

London (Biol), 263, 1745-1750.

Maguire, E.A., Burgess, N., Donnett, J.G., Frackowiak, R.S.J., Frith, C.D., & O'Keefe, J. (1998). Knowing where and getting there: A human navigation network. *Science, 280,* 921-924.

Maguire, E.A., Frackowiack, R.S.J., & Frith, C.D. (1996). Learning to find your way: a role for the human hippocampal region. *Proceedings of the Royal Society of London (Biol), 263,* 1745-1750.

Maguire, E.A., Frackowiack, R.S.J., & Frith, C.D. (1997). Recalling routes around London: Activation of the right hippocampus in taxi drivers. *The Journal of Neuroscience, 17(18),* 7103-7110.

Malinowski, J.C. & Gillespie. W.T. (2001). Individual differences in performance on a large-scale, real-world wayfinding task. *Journal of Environmental Psychology, 21,* 73-82.

Martin, J.A., Hamilton, B.E., Sutton, P.D., Ventura, S.J. et al. (2009). Final data for 2006. *National Vital Statistics Report, 57(7)*. Hyattsville, MD: National Center for Health Statistics.

Martino, M.A., Nevadunsky, N., Magliaro, T.J., & Goldberg, M.I. (2002). The DES

(Diethylstilbestrol) years: Bridging the past into the future. *Primary Care Update, 9,* 7-12.

Masica. D.N., Money, J., Ehrhardt, A.A., & Lewis, V.G. (1969). IQ, fetal sex hormones and cognitive patterns: Studies in the testicular feminizing syndrome of androgen insensitivity. *Johns Hopkins Medical Journal, 124(1),* 34-43.

Mastorakos, G., Lambrinoudaki, I., & Creatsas, G. (2006). Polycystic ovary syndrome in adolescents: current and future treatment options. *Paediatric Drugs, 8(5),* 311-318.

Matarazzo, J.D. (1972). *Wechsler's measurement and appraisal of adult intelligence.* Baltimore: Williams and Wilkins.

McBurney, D.H., Gaulin, S.J.C., Devineni, T., & Adams, C. (1997). Superior spatial memory of women: Stronger evidence for the gathering hypothesis. *Evolution and Human Behavior, 18(3),* 165-174.

McCarthy, M.M. & Arnold, A.P. (2008). Sex differences in the brain: What's old and what's new. In J.B. Becker, K.J. Berkley, N. Geary, E. Hampson, J.P. Herman, & E.A. Young (Eds.), *Sex differences in the brain: from genes to behavior.* (pp. 15-33). New York: Oxford University Press.

McCormick, C.M. & Witelson, S.F. (1991). A cognitive profile of homosexual men compared to heterosexual men and women. *Psychoneuroendocrinology, 15,* 459-473.

McEwen, B.S. (1980). Gonadal steroids and brain development. *Biology Reproduction, 22,* 43-48.

McEwen, B.S. (1981). Sexual differentiation of the brain. *Nature, 292(2),* 57-58.

McEwen, B.S., Lieberburg, I., Chaptal, C., & Krey, L.C. (1977). Aromatization: important for sexual differentiation of the neonatal rat brain. *Hormones and Behavior, 9,* 249-263.

McKeever, W.F. & Deyo, R.A. (1990). Testosterone, dihydrotestosterone, and spatial task performance of males. *Bulletin of the Psychonomic Society, 28(4),* 305-308.

McKeever, W.F., Rich, D.A., Deyo, R.A., & Conner, R.L. (1987). Androgens and spatial ability: Failure to find a relationship between testosterone and ability measures. *Bulletin of the Psychonomic Society, 25,* 438-440.

Meikle, A.W., Stringham, J.D., Bishop, D.T., & West, D.W. (1988). Quantitating genetic and nongenetic factors influencing androgen production and clearance rates in men. *Journal of Clinical Endocrinology and Metabolism, 67,* 104-109.

Mendelson, C.R. (2004). Mechanisms of hormone action. In J.E. Griffin & S.R. Ojeda (Eds.), *Textbook of Endocrine Physiology* (pp. 49-88). New York: Oxford University Press.

Michel, C.M., Kaufman, L., & Williamson, S.J. (1994). Duration of EEG and MEG α suppression increases with angle in a mental rotation task. *Journal of Cognitive Neuroscience, 6(2),* 139-150.

Moffat, S.D., Zonderman, A.B., Metter, E.J., Blackman, M.R., Harman, S.M. & Resnick, S.M. (2002). Longitudinal assessment of serum free testosterone concentration predicts memory performance and cognitive status in elderly men. *The Journal of Clinical Endocrinology and Metabolism, 87(11),* 5001-5007.

Moffat, S.D., & Hampson, E. (1996). A curvilinear relationship between testosterone and

spatial cognition in humans: Possible influence of hand preference. *Psychoneuroendocrinology, 21(3),* 323-337.

Moffat, S.D. & Hampson, E. (2000). Salivary testosterone concentrations in left-handers : An association with cerebral language lateralization ? *Neuropsychology, 14(1),* 71-81.

Moffat, S.D., Hampson, E., & Hatzipantelis, M. (1998). Navigation in a “virtual” maze: Sex differences and correlation with psychometric measures of spatial ability in humans. *Evolution and Human Behavior, 19,* 73-87.

Moffat, S.D. & Resnick, S.M. (2002). Effects of age on virtual environment place navigation and allocentric cognitive mapping. *Behavioral Neuroscience, 116(5),* 851-859.

Moffat, S.D., Zonderman, A.B., & Resnick, S.M. (2001). Age differences in spatial memory in a virtual environment navigation task. *Neurobiology of Aging, 22,* 787-796.

Möhlig, M., Jürgens, A., Spranger, J., Hoffmann, K., Weickert, M.O., Schlösser, H.W., et al. (2006). The AR CAG repeat modifies the impact of tesosterone on insulin resisitance in women with polycystic ovary syndrome. *European Journal of Endocrinology, 155,* 127-130.

Money, J., Alexander, D., & Walker, H. T. (1965). *A standardized road-map test of direction sense. Baltimore:* Johns Hopkins Press.

Morris, R.G.M. (1984). Developments of a water-maze procedure for studying spatial learning in the rat. *Journal of Neuroscience Methods, 11,* 47-60.

Morris, R.G.M., Garrud, P., Rawlings, J.N., & O'Keefe, J. (1982). Place navigation impaired in rats with hippocampal lesions. *Nature, 297(5868),* 681-683.

Morton, N., & Morris, R.G. (1995). Image transformation dissociated from visuospatial working memory. *Cognitive Neuropsychology, 12(7),* 767-791.

Moser, E., Moser, M.B., & Anderson, P. (1993). Spatial learning impairment parallels the magnitude of dorsal hippocampal lesions, but is hardly present following ventral lesions. *Journal of Neuroscience, 13(9),* 3916-3925.

Mueller, S.C., Jackson, C.P.T., & Skelton, R.W. (2008). Sex differences in a virtual water maze: An eye tracking and pupillometry study. *Behavioural Brain Research, 193,* 209-215.

Naftolin, F., Ryan, K.J., Davies, I.J., Reddy, V.V., Flores, F., Petro, Z. et al. (1975). The formation of estrogens by central neuroendocrine tissues. *Recent Progress in Hormone Research, 31,* 295-319.

Naghdi, N., Nafisty, N., & Majilessi, N. (2001). The effects of interhippocampal testosterone and flutamide on spatial localization in the Morris water maze. *Brain Research, 897,* 44-51.

National Institutes of Health. (2009). Androgen insensitivity syndrome. (NIH Publication http://ghr.nlm.nih.gov/condition=androgeninsensitivitysyndrome)

Neave, N., Menaged, M., & Weightman, D.R. (1999). Sex differences in cognition: The role of testosterone and sexual orientation. *Brain and Cognition, 41,* 245-262.

New, M.I., Dupont, B., Grumbach, K., & Levine, L.S. (1983). Congenital adrenal

hyperplasia and related conditions. In J.B. Stanbury, J.B. Wyngaarden, D.S. Fredrickson, J.L. Goldstein, & M.S. Brown (Eds.). *The metabolic basis of inherited disease (5th ed.),* (pp. 973-1000). New York: McGraw-Hill.

Nopoulos, P., Flaum, M., O'Leary, D., & Andreasen, N.C. (2000). Sexual dimorphism in the human brain: Evaluation of tissue volume, tissue composition and surface anatomy using magnetic resonance imaging. *Psychiatry Research: Neuroimaging, 98,* 1-13.

Nowak, N. T. & Moffat, S. D. (2011). The relationship between second to fourth digit ratio, spatial, cognition, and virtual navigation. *Archives of Sexual Behavior, 40 (3),* 575-585.

Nowak, N.T. Relationships between second to fourth digit ration (2D:4D), spatial cognition, and virtual navigation. *ProQuest,* (UMI No. 1457009).

O'Connor, D.B., Archer, J., Hair, W.M., & Wu, F.C. (2001). Activational effects of testosterone on cognitive function in men. *Neuropsychologia, 39(13),* 1385-1394.

Ogawa, S., Lee, T., Nayak, A., & Glynn, P. (1990). Oxygenation-sensitive contrast in magnetic resonance image of rodent brain at high magnetic fields. *Magnetic Resonance Imaging in Medicine, 26,* 68-78.

Ogawa, S., Tank, D.W., Menon, R., Ellermann, J.M., Kim, S.G., Merkle, H. et al. (1992). Intrinsic signal changes accompanying sensory stimulation: Functional brain mapping with magnetic resonance imaging. *Proceedings of the National Academy of Sciences, USA, 89,* 5951-5955.

O'Keefe, J. & Dostrovsky, J. (1971). The hippocampus as a spatial map: Preliminary

evidence from unit activity in the freely-moving rat. *Brain Research, 34(1),* 171-175.

O'Keefe, J., & Nadel, L. (1978). *The hippocampus as a cognitive map.* Oxford University Press.

O'Keefe, J., & Speakman, A. (1987). Single unit activity in the rat hippocampus during a spatial memory task. *Experimental Brain Research, 68(1),* 1-27.

Ohnishi, T., Matsuda, H., Hirakata, M., & Ugawa, Y. (2006). Navigation ability dependent neural activation in the human brain: An fMRI study. *Neuroscience Research, 55,* 361-369.

Pang, S., Levine, L.S., Chow, D.M., Faiman, C., & New, M.I. (1979). Serum androgen concentrations in neonates and young infants with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *Clinical Endocrinology, 11(6),* 575-584.

Pardridge, W.M. (1986). Serum bioavailability of sex steroid hormones. *Clinical Endocrinology and Metabolism, 15,* 259-278.

Parker, K.L. (2004). Sexual differentiation. In J.E. Griffin & S.R. Ojeda (Eds.), *Textbook of Endocrine Physiology* (pp. 167-185). New York: Oxford University Press.

Passini, R. (1984). Wayfinding in architecture. New York: Van Nostrand Reinhold Company Inc.

Pearce, J.M., Roberts, A.D., & Good, M. (1998). Hippocampal lesions disrupt navigation based on cognitive maps but not heading vectors. *Nature, 396(6706),* 75-77.

Perrin, J.S., Herve, P.Y., Leonard, G., Perron, M., Pike, G.B., Pitiot, A. et al. (2008).

Growth of white matter in the adolescent brain: Role of testosterone and androgen receptor. *The Journal of Neuroscience, 28(38),* 9519-9524.

Petersen, K. & Sherry, D.F. (1996). No sex difference occurs in hippocampus, food-sharing, or memory for food caches in black-capped chickadees. *Behavioural Brain Research, 79(1-2),* 15-22.

Phoenix, C.H., Goy, R.W., Gerall, A.A., Young, W.C. (1959). Organizing action of prenatally administered testosterone proprionate on the tissues mediating mating behavior in the female guinea pig. *Endocrinology, 65,* 369-382.

Platz, E.A., Rimm, E.B., Willett, W.C., Kantoff, P.W., & Giovannucci, E. (2000). *Journal of the National Cancer Institute, 92(24),* 2009-2017.

Postma, A., Meyer, G., Tuiten, A., van Honk, J., Kessels, R.P.C., & Thijssen, J. (2000). Effects of testosterone administration on selective aspects of object-location memory in healthy young women. *Psychoneuroendocrinology, 25,* 563-575.

Poucet, B. & Benhamou, S. (1997). The neuropsychology of spatial cognition in the rat. *Critical Reviews in Neurobiology, 11(2-3),* 101-120.

Poucet, B., Save, E., Lenck-Santini, P.P. (2000). Sensory and memory properties of hippocampal place cells. *Reviews in Neuroscience, 11(2-3),* 95-111.

Powell, I. J., Land, S. J., Dey, J., Heilbrun, L. K., Hughes, M. R., Sakr, W. et al. (2005). Impact of CAG repeats in exon 1 of the androgen receptor on progression after prostatectomy. *Cancer, 103(3),* 528-537.

Puts, D. A., Cárdenas, R. A., Bailey, D. H., Burriss, R. P., Jordan, C. L. J., & Breedlove, S. M. (2010). Salivary testosterone does not predict mental rotation performance in men or women. *Hormones & Behavior, 58,* 282-

289.

Puts, D.A., McDaniel, M.A., Jordan, C.L., & Breedlove, S.M. (2008). Spatial ability and prenatal androgens: Meta-analyses of congenital adrenal hyperplasia and digit ratio (2D:4D) studies. *Archives of Sexual Behavior, 37,* 100-111.

Puy, L., MacLusky, N.J., Becker, L., Karsan, N., Trachtenberg, J., & Brown, T.J. (1995). Immunocytochemical detection of AR in human temporal cortex: Characterization and application of polyclonal AR antibodies in frozen and paraffin-embedded tissues. *Journal of Steroid Biochemistry and Molecular Biology, 55(2),* 197-209.

Quigley, C.A., De Bellis, A., Marschke, K.B., El-Awady, M.K., Wilson, E.M., & French, F.S. (1995). AR defects: Historical, clinical, and molecular perspectives. *Endocrine Reviews, 16(3),* 271-321.

Quissell, D.O. (1993). Steroid hormone analysis in human saliva. *Annals of the New York Academy of Sciences, 694,* 143-145.

Raber, J., Bongers, G., LeFevour, A., Buttini, M., & Mucke, L. (2002). Androgens protect against apolipoprotein E4-induced cognitive deficits. *Journal of Neuroscience, 22,* 5204-5209.

Rahman, Q., Andersson, D., & Govier, E. (2005). A specific sexual orientation-related difference in navigation strategy. *Behavioral Neuroscience, 119(1),* 311-316.

Rahman, Q., & Koerting, J. (2008). Sexual orientation-related differences in allocentric spatial memory tasks. *Hippocampus, 18,* 55-63.

Rahman, Q. & Wilson, G.D. (2003). Large sexual orientation related differences in performance on mental rotation and judgement of line orientation.

Neuropsychology, 17, 25-31.

Rajender, S., Singh, L., & Thangaraj, K. (2007). Phenotypic heterogeneity of mutations In AR gene. *Asian Journal of Andrology, 9(2),* 147-179.

Rauchs, G., Orban, P., Balteau, E., Schmidt, C., Degueldre, C., Luxen, A. et al. (2008). Partially segregated neural networks for spatial and contextual memory in virtual navigation. *Hippocampus, 18,* 503-518.

Raynaud, J.P., Mercier-Bodard, C., & Baulieu, E.E. (1971). Rat estradiol binding plasma protein (EBP). *Steroids, 18(6),* 767-788.

Redish, A.D. (1999). *Beyond the Cognitive Map.* Cambridge, MA: The MIT Press.

Rehkämper, G., Haase, E., & Frahm, H.D. (1988). Allometric comparison of brain weight and brain structure volumes in different breeds of the domestic pigeon, Columbia livia f.d. (fantails, homing pigeons, strassers). *Brain Behavior and Evolution, 31(3),* 141-149.

Reitan, R. M. & Wolfson, D. (1985). *The Halstead-Reitan Neuropsychological Test Battery: Therapy and clinical interpretation.* Tucson, AZ: Neuropsychological Press.

Resnick, S.M., Berenbaum, S.A., Gottesman II, & Bouchard, T.J. (1986). Early hormonal influences on cognitive functioning in congenital adrenal hyperplasia. *Developmental Psychology, 22,* 191-198.

Resnick, S.M., Espeland, M.A., Jaramillo, S.A., Hirsch, C., Stefanick, M.L., Ockene, M.J. et al. (2009). Postmenopausal hormone therapy and regional brain volumes: The WHIMS-MRI study. *Neurology, 72,* 135-142.

Resnick, S.M., Maki, P.M., Rapp, S.R., Espeland, M.A., Brunner, R., Coker, L.H. et al.

(2006). Effects of combination estrogen plus progestic hormone treatment on cognition and affect. *Journal of Clinical Endocrinology and Metabolism, 91(5),* 1802-1810.

Richie, J.P. (1999). Anti-androgens and other hormonal therapies for prostate cancer. *Urology, 54,* 15-18.

Richter, W. Somorjai, R., Summers, R., Jarmasz, M., Menon, R.S., Gati, J.S. et al. (2000). Time-resolved fMRI of mental rotation. *Neuroreport, 8(17),* 3697-3702.

Riedel, G., Micheau, J., Lam, A.G., Roloff, E.L., Martin, S.J., Bridge, H. et al. (1999). Reversible neural inactivation reveals hippocampal participation in several memory processes. *Nature Neuroscience, 2(10),* 898-905.

Rissman, E.F., Heck, A.L., Leonard, J.E., Shupnik, M.A., & Gustafsson, J.A. (2002). Disruption of estrogen receptor beta gene impairs spatial learning in female mice. *Proceedings of the National Academy of Sceinces, USA, 19,* 3996-4001.

Rodgers, M.K. (2009). *The effect of age on navigation strategy.* Unpublished masters thesis. Wayne State University, Detroit.

Roof, R.L.(1993). The dentate gyrus is sexually dimorphic in prepubescent rats: Testosterone plays a significant role. *Brain Research, 610(1),* 148-151.

Roof, R.L. (1993). Neonatal exogenous testosterone modifies sex differences in radial arm and Morris water maze performance in prepubescent and adult rats. *Behavioral Brain Research, 53(1-2),* 1-10.

Roof, R.L. & Havens, M.D. (1992). Testosterone improves maze performance and induces development of a male hippocampus in females. *Brain Research, 572,* 310-313.

Roof, R.L., Zhang, Q., & Glasier, M.M. (1993). Gender-specific impairment on Morris water maze task after entorhinal cortex lesion. *Behavioral Brain Research, 57(1), 57-51,* 47-51.

Roseli, C.E. (1991). Sex differences in ARs and aromatase activity in microdissected regions of the rat brain. *Endocrinology, 128,* 1310-1316.

Roseli, C.E., Handa, R.J., & Resko, J.A. (1989). Quantitative distribution of nuclear ARs in microdissected areas of the rat brain. *Neuroendocrinology, 49(5),* 449-453.

Rosen, M.P. & Cedars, M.I. (2004). Female reproductive endocrinology and infertility. In D.G. Gardner & D. Schoback, D. (Eds.) *Greenspan's Basic and Clinical Endocrinology* (8th ed.). (pp. 502-561). Chicago: McGraw Hill.

Rosenfield, R.L., Barnes, R.B., Cara, J.F., & Lucky, A.W. (1990). Dysregulation of cytochrome P450c 17 alpha as the cause of polycystic ovarian syndrome. *Fertility and Sterility, 53,* 785-791.

Rosner, W. (2001). An extraordinarily inaccurate assay for free testosterone is still with us. *Journal of Clinical Endocrinology and Metabolism, 86(6),* 2903.

Rosner, W., Auchus, R. J., Azziz, R., Sluss, P. M, & Raff, H. (2007). POSITION STATEMENT: Utility, Limitations, and Pitfalls in Measuring Testosterone: An Endocrine Society Position Statement. *Journal of Clinical Endocrinology and Metabolism, 92(2),* 405-13.

Rosner, W. & Vesper, H. (2008). CDC workshop report improving steroid hormone measurements in patient care and research translation. *Steroids.* doi:10.1016/j.steroids.2008.08.001

Rovine, M.J., & Weisman, G.D. (1989). Sketch-map variables as predictors of way-finding performance. *Journal of Environmental Psychology, 9(3),* 217-232.

Rubinow, D.R., & Schmidt, P.J. (1996). Androgens, brain, and behavior. *Hormones and Behavior, 153,* 974-984.

Ryan, B.C. & Vandenbergh, J.G. (2002). Intrauterine position effects. *Neuroscience and Biobehavioral Studies, 26(6),* 665-678.

Salhouse, T.A. (1994). The aging of working memory. *Neuropsychology, 8(4),* 535-543.

Sanders, G. & Ross-Field, L. (1986). Sexual orientation and visuo-spatial ability. *Brain and Cognition, 5,* 280-290.

Sandstrom, N.J., Kaufman, J., & Huettel, S. (1998). Males and females use different distal cues in a virtual environment navigation task. *Cognitive Brain Research, 6,* 351-360.

Sandstrom, N.J., Kim, J.H., & Wasserman, M.A. (2006). Testosterone modulates performance on a spatial working memory task in male rats. *Hormones and Behavior, 50(1),* 18-26.

Sar, M. & Stumpf, W.E. (1975). Distribution of androgen concentrating neurons in rat brain. In W.E. Stumpf & L.D. Grant (Eds.). *Anatomical Neuroendocrinology,* (pp. 120-133). Basel: Karger.

Sarrieau, A., Mitchell, J.B., Lal, S., Olivier, A., Quirion, R., & Meaney, M.J. (1990). Androgen binding sites in human temporal cortex. *Neuroendocrinology, 51,* 713-716.

Saucier, D.M., Green, S.M., Leason, J., MacFadden, A., Bell, S., & Elias, L. (2002). Are sex differences in navigation caused by sexually dimorphic strategies or by

differences in ability to use the strategies? *Behavioral Neuroscience, 116(3),* 403-410.

Save, E., & Poucet, B. (2000). Hippocampal-parietal cortical interactions in spatial cognition. *Hippocampus, 10(4),* 491-499.

Save, E., & Poucet, B. (2000). Involvement of the hippocampus and associative parietal cortex in the use of proximal and distal landmarks for navigation. *Behavioral Brain Research, 109(2),* 195-206.

Schattmann, L. & Sherwin, B.B. (2007). Effects of the pharmacologic manipulation of testosterone on cognitive functioning in women with polycystic ovary syndrome: A randomized, placebo-controlled treatment study. *Hormones and Behavior, 51,* 579-586.

Schattmann, L. & Sherwin, B.B. (2007). Testosterone levels and cognitive functioning in women with polycystic ovary syndrome and in healthy young women. *Hormones and Behavior, 51,* 587-596.

Schöning, S., Engelien, A., Kugel, H., Schäfer, S., Schiffbauer, H., Zwitserlood, P. et al. (2007). Functional anatomy of visuo-spatial working memory during mental rotation is influenced by sex, menstrual cycle, and sex steroid hormones. *Neuropsychologia, 45,* 3203-3214.

Shah, N.A., Antoine, H.J., Pall, M., Taylor, K.D., Azziz, R., & Goodzari, M.O. (2008). Association of AR CAG repeat polymorphism and polycycstic ovary syndrome. *Journal of Clinical Endocrinology and Metabolism, 93(5),* 1939-1945.

Sherry, D.F., Jacobs, L.F., & Gaulin, S.J.C. (1992). Spatial memory and adaptive

specialization of the hippocampus. *TINS, 15(8),* 298-303.

Shipman, S.L. & Astur, R.S. (2008). Factors affecting the hippocampal BOLD response during spatial memory. *Behavioural Brain Research, 187,* 433-441.

Shute, V.J., Pellegrino, J.W., Hubert, L., & Reynolds, R.W. (1983). The relationship between androgen levels and human spatial abilities. *Bulletin of the Psychonomic Society, 21(6),* 465-468.

Silverman, I., & Eals, M. (1992). Sex differences in spatial abilities: Evolutionary theory and data. In J.H. Barkow, L. Cosmides, & J. Tooby (Eds.), *The adapted mind: Evolutionary psychology and the generation of culture.* New York: Oxford University Press.

Silverman, I., Kastuk, D., Choi, J., & Phillips, K. (1999). T levels and spatial ability in men, *Psychoneuroendocrinology, 24,* 813-822.

Simmons, Z. L. & Roney, J. R. (2011). Variation in CAG repeat length of the androgen receptor gene predicts variables associated with intrasexual competitiveness in human males. *Hormones and Behavior, 60,* 306-312.

Singh, R. J. (2008). Validation of a high throughput method for serum/plasma testosterone using liquid chromatography tandem mass spectrometry (LC-MS/MS). *Steroids.* doi:10.1016/j.steroids.2008.07.006

Smail, P.J., Reyes, F.I., Winter, J.S.D., & Faiman, C. (1981). The fetal hormone environment and its effect on the morphogenesis of the genital system. In S.J. Kogan & E.S.E. Hafez (Eds.), *Pediatric Andrology*. The HagueL Martinus Nijhoff.

Smals, A.G.H., Klopenborg, P.W.C., & Benraad, T.J. (1976). Circannual cycle in plasma

testosterone levels in man. *Journal of Clinical Endocrinology and Metabolism, 42,* 979-982.

Spritzer, M.D., Gill, M., Weinberg, A., & Galea, L.A. (2008). Castration differentially affects spatial working and reference memory in male rats. *Archives of Sexual Behavior, 37(1),* 19-29.

Stanczyk, F.Z. (2006). Measurement of androgens in women. *Seminars in Reproductive Medicine, 24(2),* 78-85.

Stanczyk, F. Z., Lee, J. S., & Santen, R. J. (2007). Standardization of steroid hormone assays: Why, how, and when? *Cancer Epidemiology, Biomarkers & Prevention*, *16(9),* 1713-19.

Stein, I.F. & Leventhal, M.L. (1935). Amenorrhea associated with bilateral polycystic ovaries. *American Journal of Obstertrics and Gynecology, 29,* 181-191.

Stewart, J., Skvarenina, A., & Pottier, J. (1975). Effects of neonatal androgens on open-field behavior and maze learning in the prepubescent and adult rat. *Physiology and Behavior, 14,* 291-295.

Swartz, S.K., & Soloff, M.S. (1974). The lack of estrogen binding by human alpha fetoprotein. *Journal of Clinical Endocrinology and Metabolism, 39,* 589-591.

Tagaris, G.A., Kim, S.G., & Strupp, J.P. (1996). Quantitative relations between parietal activation and performance in mental rotation. *Neuroreport, 7(3),* 773-773.

Tagaris, G.A., Richter, W., & Kim, S.G. (1998). Functional magnetic resonance imaging of mental rotation and memory scanning: a multifunctional scaling analysis of brain activation patterns. *Brain Research reviews, 26(2-3),* 106-112.

Taieb, J., Mathian, B., Millot, F., Patricot, M-C., Mathieu, E., Queyrel, N. et al. (2003).

Testosterone measured by 10 immunoassays and by isotope-dilution gas chromatography-mass spectrometry in sera from 116 men, women, and children. *Clinical Chemistry, 49(8),* 1381-1395.

Takeuchi, Y. (1992). Sense of direction and its relationship with geographical orientation, personality traits and mental ability. *Japanese Journal of Educational Psychology, 40,* 47-53.

Taylor, R. N. & Lebovic, D. I. (2007). The Endocrinology of Pregnancy. In D. G. Gardner & D. Shoback (Eds.), *Greenspan's Basic & Clinical Endocrinology (8th ed.).* (pp. 641-660). New York: McGraw Hill.

Thilers, P.P. MacDonald, S.W.S., & Herlitz, A. (2006). The association between endogenous free testosterone and cognitive performance: A population-based study in 35 to 90 year-old men and women. *Psychoneuroendocrinology, 31,* 565-576.

Thomsen, T., Hugdahl, K., Ersland, L., Barndon, R., Lundervold, A., Smievoll, A.I. et al. (2000). Functional magnetic resonance imaging (fMRI) study of sex differences in a mental rotation task. *Medical Science Monitor, 6(6),* 1186-1196.

Tohgi, H., Utsugisawa, K., Yamagata, M. & Yoshimura, M. (1995). Effects of age on messenger RNA expression of glucocorticoid, thyroid hormone, androgen, and estrogen receptors in postmortem human hippocampus. *Brain Research, 700(1-2),* 245-253.

Tomasino, B. & Rumiati, R.I. (2004). Effects of strategies on mental rotation and hemispheric lateralization: neuropsychological evidence. *Journal of Cognitive Neuroscience, 5,* 878-888.

Torpy, J.M., Lynm, C., & Glass, R.M. (2007). JAMA patient page. Polycysitc ovary syndrome. *Journal of the American Medical Association, 297(5),* 554.

Tuiten, A., Van Honk, J., Koppeschaar, H., Bernaards, C., Thijssen, J., & Verbaten, R. (2000). Time course of effects of testosterone administration on sexual arousal in women. *Archives of General Psychiatry, 57(2),* 155-156.

Tut, T.G., Ghadessy, F.J., Trifiro, M.A., Pinsky, L., & Yong, E.L. Long polyglutamine tracts in the AR are associated with reduced transactivation, impaired sperm production and male infertility. *Journal of Clinical Endocrinology and Metabolism, 82,* 3777-3782.

Ullman, M.T., Miranda, R.A., & Travers, M.L. (2008). In J.B. Becker, K.J. Berkley, N. Geary, E. Hampson, J.P. Herman, & E.A. Young (Eds.), *Sex differences in the brain: from genes to behavior.* (pp. 291-309). New York: Oxford University Press.

van Anders, S.M. & Hampson, E. (2005). Testing the prenatal androgen hypothesis: Measuring digit ratios, sexual orientation, and spatial abilities in adults. *Hormones and Behavior, 47,* 92-98.

van Anders, S.M., Hampson, E. & Watson, N.V. (2006). Seasonality, waist-to-hip ratio, and salivary testosterone. *Psychoneuroendocrinology, 31,* 895-899.

Van de Beek, C., Thijssen, J.H.H., Cohen-Kettenis, P.T., Van Goozen, S.H.M., & Buitelaar, J.K. (2004). Relationships between sex hormones assessed in amniotic fluid, and maternal and umbilical cord blood: what is the best source of information to investigate the effects of fetal hormonal exposure? *Hormones and Behavior, 46,* 663-669.

Vandenberg, S.G. & Kuse, A.R. (1978). Mental rotations: A group test of three-

dimensional spatial visualization. *Perceptual Motor Skills, 47,* 599-601.

Vandenberg, S.G., Kuse, A.R., & Vogler, G.P. (1985). Searching for correlates of spatial ability. *Perceptual and Motor Skills, 60,* 343-350.

Van Honk, J., Tuiten, A., Verbaten, R., van den Hout, M., Koppeschaar, H., Thijssen, J. et al. (1999). Correlations among salivary T, mood, and selective attention to threat in humans. *Hormones and Behavior, 36(1),* 17-24.

Van Kesteren, P.J., Gooren, L.J., Megens, J.A. (1996). An epidemiological and demographic study of transsexuals in The Netherlands. *Archives of Sexual Behavior, 25(6),* 589-600.

Vecchi, T. & Girelli, L. (1998). Gender differences in visuo-spatial processing: the importance of distinguishing between passive storage and active manipulation. *Acta Psychologia,* 1-16.

Vermeulen, A., Verdonck, L., & Kaufman, J.M. (1999). A critical evaluation of simple methods for the estimation of free testosterone in serum. *The Journal of Clinical Endocrinology and Metabolism, 84(10),* 3666-3672.

Vingerhoets, G., de Lange, F.P., Vandemaele, P., Deblaere, K., & Achten, E. (2002). Motor imagery in mental rotation: an fMRI study. *NeuroImage, 17(3),* 1623-1633.

Vining, R.F. & McGinley, R.A. (1986). Hormones in saliva. *Critical reviews in clinical laboratory sciences, 23(2),* 95-146.

Vittek, J., L'Hommedieu, D.G., Gordon, G.G., Rappaport, S.C., & Southren, A.L. (1985). Direct radioimmunoassay (RIA) of salivary testosterone: correlation with free and total serum testosterone. *Life Sciences, 37(8),* 711-716.

vom Saal, F.S. & Bronson, F.H. (1978). In utero proximity of female mouse fetuses to males: effects on reproductive performance during later life. *Biology of Reproduction, 19,* 842-853.

vom Saal, F.S., Quadagno, D.M., Even, M.D., Keisler, L.W., Keisler, D.H., & Khan, S. (1990). Paradoxical effects of maternal stress on fetal steroids and postnatal reproductive traits in female mice from different intrauterine positions. *Biology of Reproduction, 43,* 751-761.

Voyer, D., Voyer, S., & Bryden., M. (1995). Magnitude of sex differences in spatial abilities: A meta-analysis and consideration of critical variables. *Psychological Bulletin, 117(2),* 250-270.

Wang, C., Catlin, D.H., Demers, L.M., Starcevic, B., & Swerdloff, R.S. (2004). Measurement of total serum testosterone in adult men: Comparison of current laboratory methods versus liquid chromatography-tandem mass spectrometry. *The Journal of Clinical Endocrinology and Metabolism, 89(2),* 534-543.

Wang, C., Plymate, S., Nieschlag, E., & Paulsen, C.A. (1981). Salivary testosterone in men: further evidence of a direct correlation with free serum T. *Journal of Clinical Endocrinology and Metabolism, 53,* 1021-1024.

Ward, S.L., Newcombe, N., & Overton, W.F.(1986). Turn left at the church, or three miles north. *Environment and Behavior, 18(2),* 192-213.

Wechsler, D. (1981). *Manual for the Wechsler Adult Intelligence Scale-Revised.* New York: The Psychological Corporation.

Wechsler Test of Adult Reading (2001). *Wechsler Test of Adult Reading Manual.* San Antonio, TX: The Psychological Corporation.

Wegesin, D.J. (1998). A neuropsychologic profile of homosexual and heterosexual men and women. *Archives of Sexual Behavior, 27,* 91-108.

Weiss, E., Siedentopf, C.M., Hofer, A., Deisenhammer, E.A., Hoptman, M.J., Kremser, C. et al. (2003). Sex differences in brain activation pattern during a visuospatial cognitive task: a functional magnetic resonance imaging study in healthy volunteers. *Neuroscience Letters, 344,* 169-172.

Westberg, L., Baghael, F., Rosmond, R., Hellstrand, M., Landen, M., Jansson, M. et al. (2001). Polymorphisms of the AR gene and the estrogen receptor β gene are associated with androgen levels in women. *Journal of Clinical Endocrinology and Metabolism, 86(6),* 2562-2568.

Wheeler, M.J. (1987). Warning on serum testosterone measurement. *The Lancet (British Edition), 2,* 514-515.

Wiegratz, I., Jung-Hoffmann, C., & Kuhl, H. (1995). Effect of two oral contraceptives containing ethynalestradiol and gestodene or norgestimate upon androgen parameters and serum binding proteins. *Contraception (51),* 341-346.

Williams, C.L., Barnett, A.M., & Meck, W.H. (1990). Organizational effects of early gonadal secretions on sexual differentiation in spatial memory. *Behavioral Neuroscience, 104,* 84-97.

Wilson, C.A. & Davies, D.C. (2007). The control of sexual differentiation of the reproductive system and brain. *Reproduction, 133(2),* 331-359.

Wilson, E.M. & French, F.S. (1976). Binding properties of ARs: evidence for identical receptors in rat testis, epididymis and prostate. *Journal*

of Biological Chemistry, 251, 5620-5629.

Winson, J. (1978). Loss of hippocampal theta rhythm results in spatial memory deficit in the rat. *Science, 210(4351),* 160-163.

Wisniewski, A.B., Nguyen, T.T., & Dobs, A.S. (2002). Evaluation of high-dose estrogen and high-dose estrogen plus methyltestosterone treatment on cognitive task performance in postmenopausal women. *Hormone Research, 58,* 150-155.

Wolf, O.T., Preut, R., Hellhammer, D.H., Kudielka, B.M., Schurmeyer, T.H., & Kirschbaum, C. (2000). T and cognition in elderly men: A single T injection blocks the practice effect in verbal fluency, but has no effect on spatial or verbal memory. *Biological Psychiatry, 47(7),* 650-654.

Xiao, L., & Jordan, C.L. (2002). Sex differences, laterality, and hormonal regulation of AR immunoreactivity in rat hippocampus. *Hormones and Behavior, 42,* 327-336.

Yaffe, K., Edwards, E.R., Lui, L.Y., Zmuda, J.M., Ferrell, R.E., & Cauley, J.A. (2003). AR CAG repeat polymorphism is associated with cognitive function in older men. *Biological Psychiatry, 54(9),* 943-946.

Yeap, B.B. (2009). Are declining testosterone levels a major risk factor for ill-health in aging men? *International Journal of Impotence Research,21,* 24-36.

Yonker, J.E., Eriksson, E., Nilsson, L.G., Herlitz, A. (2006). Negative association of testosterone on spatial visualization in 35 to 85 year old men. *Cortex,42,* 376-386.

Zuloaga, D.G., Puts, D.A., Jordan, C.L., & Breedlove, M.S. (2008). The role of ARs in the masculinization of brain and behavior: what we've

learned from the testicular feminization mutation. *Hormones and Behavior, 53 (5),* 613-626.

Zumoff, B., Strain, G.W., Miller, L.K., & Rosner, W. (1995). Twenty-four-hour mean plasma testosterone concentration declines with age in normal premenopausal women. *The Journal of Clinical Endocrinology and Metabolism, 80(4),* 1429-1430.

ABSTRACT

EFECTS OF SEX, FREE TESTOSTERONE, AND ANDROGEN RECEPTOR CAG REPEAT NUMBER ON SPATIAL COGNITION AND VIRTUAL NAVIGATION PERFORMANCE

by

NICOLE T. NOWAK

May 2012

Advisor: Dr. Scott D. Moffat

Major: Psychology (Behavioral and Cognitive Neuroscience)

Degree: Doctor of Philosophy

The male advantage typically found on some measures of spatial cognition (e.g., mental rotations) has been approached for three decades from the perspective that androgens contribute to this sex difference. To date, evidence to support the notion that androgens affect spatial cognition in healthy young individuals is balanced by evidence to the contrary. The present study sought to clarify the association between androgens and spatial performance by extending our measurements of androgenicity to include both a measure of circulating testosterone as well as a receptor-specific marker.

The aims of this dissertation were to assess the effects of sex, testosterone, and androgen receptor CAG repeat number on spatial performance and experience in a group of healthy young men and women. The hypothesis that men would outperform women on measures of spatial skills was largely supported, with some caveats. Predictions that testosterone would relate directly to spatial performance were not confirmed; however, results indicate that number of CAG repeats may have a direct impact on cognition, and may modify the relationship between testosterone and spatial

cognition within sex. Future research with larger samples of men and women is needed to clarify the significance of the patterns reported from these initial observations.

AUTOBIOGRAPHICAL STATEMENT

Nicole T. Nowak

Education

2012	Wayne State University, Detroit, Michigan; Ph.D. in Psychology (Behavioral and Cognitive Neuroscience)
2008	Wayne State University, Detroit, Michigan; M.A. in Psychology (Behavioral and Cognitive Neuroscience)
2001	University of Minnesota Duluth, Duluth, Minnesota; B.A.S. in Psychology