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Sex differences in visuospatial abilities persist during induced hypogonadism

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Abstract

Background—Despite well-established sex differences in the performance on tests of several cognitive domains (e.g., visuospatial ability), few studies in humans have evaluated if these sex differences are evident both in the presence of circulating sex hormones and during sex steroid hormonal suppression. Sex differences identified in the relative absence of circulating levels of estradiol and testosterone suggest that differences in brain structure or function exist independent of current hormonal environment and are more likely a reflection of differing developmental exposures and/or genetic substrates.

Objective—To evaluate cognitive performance in healthy eugonadal men and women before and again during GnRH agonist-induced hypogonadism.

Methods—Men (n = 16) and women (n = 15) without medical or psychiatric illness were matched for IQ. Cognitive tests were performed at baseline (when eugonadal) and after 68 weeks of GnRH agonist-induced gonadal suppression. The test batteries included measures of verbal and spatial memory, spatial ability, verbal fluency, motor speed/dexterity, and attention/concentration. Data were analyzed using repeated-measures models.

Results—During both eugonadism and hypogonadism, men performed significantly better than women on several measures of visuospatial performance including mental rotation, line orientation, Money Road Map, Porteus maze, and complex figure drawing. Although some test performances showed an effect of hormone treatment, the majority of these differences reflected

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an improved performance during hypogonadism compared with baseline (and probably reflected practice effects).

Conclusion—The well-documented male advantage in visuospatial performance, which we observed during eugonadal conditions, was maintained in the context of short-term suppression of gonadal function in both men and women. These findings suggest that, in humans, sex differences in visuospatial performance are not merely dependent on differences in the current circulating sex steroid environment. Thus sex differences in visuospatial performance in adulthood could reflect early developmental effects of sex steroid exposure or other environmental exposures differing across the sexes as our data confirm that these differences are independent of circulating estradiol or testosterone levels in men and women.

Keywords

Sex differences; Sex steroids; Hypogonadism; Mental rotation; Visuospatial

1. Introduction

Despite evidence of both sex differences and sex steroid-related changes in the performances on tests of several cognitive domains (e.g., visuospatial ability), few studies in humans have determined whether those sex differences are evident both in the presence of circulating sex hormones and in hypogonadal states. A differential performance during hypogonadal compared with the eugonadal states would potentially indicate the activational effects of current brain hormonal environment on cognitive performances. In contrast, differences between women and men also present in the relative absence of circulating levels of estradiol and testosterone, respectively may suggest more enduring sex differences in brain structure/organization or function reflecting differences in developmental exposures and/or genetic substrate.

Our understanding of the role of sex steroids in cognitive performance has been informed by both in vitro and in vivo animal and human studies. Preclinical observations include the following: sex differences in performance of cognitive tasks (presumed consequent to differences in sex steroid levels or exposure); changes in the performance on cognitive measures across the estrus cycle or after sex steroid manipulations; reversal by sex steroids of induced cognitive deficits; regulation by sex steroids of systems critical for cognition; and protection by sex steroids of neurons in vitro against a variety of insults (Peterson et al., 1992; Shors et al., 1998; McEwen, 2002; Behl, 2002; Rapp et al., 2003; Lacreuse et al., 2004; Gibbs, 2000). Studies in humans complement these pre-clinical findings. First, sex differences have been replicated in the performance of a range of cognitive tasks (motor dexterity, articulatory speed, visuospatial ability) (Kimura, 1987; Duff and Hampson, 2001; Jones et al., 2003; McCarthy and Konkle, 2005). Second, performance on several cognitive measures varies across the menstrual cycle (e.g., motor dexterity, verbal fluency, visuospatial ability, implicit memory) (Hampson and Kimura, 1988; Maki et al., 2002) and correlates with levels of circulating sex steroids. Third, cognitive changes are observed after manipulations of sex steroids in both women and men (Sherwin and Tulandi, 1996; Grigorova et al., 2006; Cherrier et al., 2008). Fourth, albeit controversial, sex steroids have putative benefits in the treatment of cognitive dysfunction (acute and prophylactic effects) in

some studies (LeBlanc et al., 2001; Yaffe et al., 1998; Cherrier et al., 2001; Wolf et al., 1999; Maki et al., 2001; Joffe et al., 2006; Smith et al., 2001; Cherrier, 2009; Cherrier et al., 2005). Finally, a role for sex steroids in cognition is also suggested by demonstrations of the modulatory effects of sex steroids on cerebral blood flow (Berman et al., 1997; Shaywitz et al., 1999; Goldstein et al., 2005; Protopopescu et al., 2005; Smith et al., 2006; van Wingen et al., 2007) as well as on mood (Schmidt et al., 1998) in subgroups of women.

While the observed differences in cognitive test performance seen in association with changes in levels of sex hormones or across sexes may be directly mediated by sex hormones, co-occurrence does not imply causality. Given the many hormones that change during the menstrual cycle, the naturalistic setting within which many studies are conducted precludes the isolation of the relevant variables (and the exclusion of other variables) that could affect both hormone levels and cognition. Similarly, observations of improved cognitive performance after hormonal treatment of a medical or gynecologic condition cannot be generalized to healthy subjects. Finally, differing ages of study participants introduces additional sources of variation among studies, as age may alter both baseline cognitive performance and the observed effects of sex steroids on these measures (Voytko, 2000; Rapp et al., 2002).

Among reported sex differences in cognitive performance, the male advantage in mental rotation remains one of the most widely replicated findings in human studies (Peters et al., 1995; Voyer et al., 1995; Linn and Petersen, 1985; Weiss et al., 2003; Koscik et al., 2009; Astur et al., 2004; Parsons et al., 2004), though not all studies of mental rotation have demonstrated this male advantage in task performance (Dietrich et al., 2001; Thomsen et al., 2000; Jordan et al., 2002; Tagaris et al., 1996; Hugdahl et al., 2006). Furthermore, some studies have reported that the modulatory effects of sex steroids might be responsible for observed differences in visuospatial performance between women and men (Mäntylä, 2013; Courvoisier et al., 2013; Thilers et al., 2006).

As part of a larger hormone manipulation protocol to identify the direct effects of sex steroids on mood, we administered a battery of cognitive tasks to healthy women and men before and after temporary suppression of circulating sex steroid secretion by the ovaries and testes in women and men, respectively. Employing a model similar to that used in animal studies, we had the opportunity to ask the question “do sex-differences in cognitive task performance observed under eugonadal conditions persist under conditions of induced hypogonadism (i.e., exist independent of the presence of sex differences in gonadal sex steroids)?”

2. Methods

2.1. Participant selection

Healthy women and men between the ages of 23 and 49 years were recruited through advertisements in the hospital newsletter. Each participant was medication free (including hormonal contraceptive agents or other forms of hormonal therapy) and was screened for the absence of significant medical or gynecologic illness through history, physical examination, and laboratory tests. All women and men were administered the Structured Clinical

Interview (Spitzer et al., 1990) to confirm the absence of current or past psychiatric illness. Written informed consents were obtained from all participants prior to study participation in this NIMH Intramural Research Review Board-approved protocol, which was part of a larger study that involved sex-steroid add-back following gonadal suppression with a gonadotropin releasing hormone (GnRH) agonist. Subjects were compensated for their participation in accordance with NIH guidelines.

2.2. Protocol

2.2.1 Hormone manipulation—Women received depot Lupron (leuprolide acetate, TAP Pharmaceuticals, Chicago, IL), 3.75 mg, by intramuscular (IM) injection every four weeks (for five to six months as part of the larger protocol). Men received depot Lupron, 7.5 mg IM, every four weeks (for 3 months as part of the larger protocol). Lupron is a depot preparation of the GnRH agonist leuprolide acetate which when administered once a month, results in a temporary suppression of gonadal function. After the initial injection of Lupron, and following an initial increase in gonadal activity, levels of pituitary gonadotropins decline and sex steroid levels decrease to approximate those observed after castration. The most common side effects of Lupron are hot-flushes in men and hot-flushes and vaginal dryness in women (Santen and Warner, 1985; Wilson et al., 2007).

2.2.2 Procedures—Cognitive testing was performed twice in both men and women and at the same time intervals relative to Lupron treatment: first when participants were eugonadal (at baseline before the hormone manipulation) and a second time between six to eight weeks of GnRH agonist-induced hypogonadism. Each of the cognitive test batteries was administered in a 2-h session. In women, the baseline cognitive tests were administered randomly across the menstrual cycle and then tests were repeated after women received Lupron (during weeks 68 of treatment). In the original study design, after baseline testing, and one month of Lupron, each man was randomly assigned to receive either testosterone or placebo replacement. Thus, to ensure that the duration of GnRH agonist-induced hypogonadism was similar between men and women for this current study, we selected only those men who received placebo replacement after the first month of Lupron (i.e., each man was studied 68 weeks of treatment). Thus in both men and women the second testing session was between 6 and 8 weeks after Lupron treatment. The severity of mood symptoms was monitored by the self-administered Beck Depression Inventory (BDI) (Beck et al., 1961). The presence and severity of daytime and nighttime hot-flushes, at baseline and during the hypogonadal state, were measured with a 6-point, daily hot-flush rating scale (Endicott et al., 1981) that was a modification of the Daily Rating Form (DRF). Those women and men who had a weekly average hot-flush symptom severity score ≥ 2 (minimal) during hypogonadism were classified as having clinically-significant hot-flushes.

Blood samples were drawn at the time of cognitive testing and were assayed for estradiol, progesterone, and total testosterone. Hormone levels were measured in order to confirm that a hypogonadal state had been obtained relative to baseline measures. The blood samples were centrifuged and aliquots of blood were frozen at −20 °C until the time of assay. In women, plasma estradiol and progesterone levels were measured with radioimmunoassay (RIA) after extraction chromatography by Esoterix (Calabassa Hills, CA). The intra-assay

coefficients of variation for estradiol and progesterone were 5.5%, and 7.5%, respectively. The inter-assay coefficients of variation for estradiol and progesterone were 10.9% and 5.8%, respectively. In men, estradiol levels were measured with RIA by Quest Diagnostics (Baltimore, MD) with an intra-assay and inter-assay coefficient of variation of 7.7% and 11.0%, respectively. In both men and women, plasma total testosterone levels were measured with equilibrium dialysis with extraction by Endocrine Sciences (Calabasas Hills, CA). In men, the intra-assay and inter-assay coefficients of variation for total testosterone were 5.7% and 14.0%, respectively. In women, the intra-assay and inter-assay coefficients of variation for total testosterone were 6.6% and 8.9%, respectively. The levels of these hormones were employed only to confirm that gonadal suppression was achieved while each participant was receiving Lupron compared with baseline. Additionally, given the limitations of RIA for measuring low circulating levels of estradiol and testosterone (i.e. during hypogonadism when peripheral levels are near the lower limits of detectability of the assays), these measures could not be employed to examine a specific relationship between estradiol or testosterone levels and cognitive performance (Rosner et al., 2007a; Rosner et al., 2007b).

2.3. Outcome measures

General cognitive ability was determined by the Wide Range Achievement Test (WRAT-R) (Jastak and Wilkinson, 1984). The cognitive tasks were selected on the basis of published evidence suggesting that the performance on each test either differed between men and women or was modulated by sex steroids and included the following domains: (1) memory (verbal and visual), (2) visuospatial ability, (3) verbal fluency, (4) motor speed and dexterity, and (5) attention and concentration. The tasks used to test those domains were as follows: Rey Complex Figure drawing (Corwin and Bylsma, 1993), Paragraph memory (logical memory test) (Talland, 1965; Wechsler, 1981; Lezak, 1995), Line Orientation (Benton et al., 1983), Mental Rotation (figure rotation) (Vandenberg and Kuse, 1978), Embedded figures (hidden figures) (Spreen and Benton, 1969), Money Road Map (Money, 1976), Porteus maze (Porteus, 1959), Verbal Fluency (Benton et al., 1983), Stroop color naming (Stroop, 1935), Purdue Pegboard (Spreen and Strauss, 1991), Grooved Pegboard (Harley et al., 1980), Finger tapping (Reitan and Wolfson, 1993), Digit Span (Wechsler, 1981), Symbol Digit modalities (Smith, 1982), and Trail Making Test (Reitan and Wolfson, 1993).

2.4. Statistical analysis

Differences in baseline characteristics including age, education, and general ability between the diagnostic groups were analyzed with Student's *t*-tests. Handedness was analyzed with a Chi square test.

Data were analyzed using SAS 9.4 statistical software (SAS Institute Inc., Cary, NC). For each of the 34 cognitive performance test scores listed in Table 2, a "best" repeated-measures statistical model (using PROC MIXED) was fitted. In order to determine differences in cognitive task performance between women and men before and after GnRH agonist-induced gonadal suppression, HORMONE condition (baseline or Lupron), SEX and the HORMONE condition-by-SEX interaction were included in all models. Two baseline

characteristics were also considered: AGE (except for the age-adjusted Mental Rotation) and EDUCATION, as well as two-way and three-way interaction terms. The "best" model was selected based on the Bayesian Information Criterion (BIC), which is closely related to the Akaike Information Criterion (AIC), but is preferred because it is subject to a greater penalty for the number of explanatory variables in the model.

For 29 of the 34 performance test scores, no explanatory variables were added (i.e., the "best" model only included HORMONE condition, SEX and HORMONE condition-by-SEX). For two test scores (Rey [delay] and Mental Rotation [total]), AGE was statistically significant and, therefore, added to the model. EDUCATION was statistically significant for two other test scores (Paragraph Memory [delay] and Porteus Maze [delay]) and was added to the model. For Symbol Digit [written], EDUCATION was not statistically significant, but the HORMONE condition-by-EDUCATION was statistically significant, and therefore, both EDUCATION and HORMONE condition-by-EDUCATION were added to the model.

The "best" model was then used to produce the Least Squares Means, standard errors, two-tailed *p*-values, effect sizes, and confidence intervals shown in Table 2. For the five test scores mentioned above, the Least Squares Means were adjusted for AGE or EDUCATION, depending on their "best" model. This adjustment cannot be derived using simpler approaches (such as paired t-tests) to compare treatments, or the average of the two scores (baseline and Lupron) to compare sexes.

The *p*-value for AGE shown in Table 2 was obtained from the model with HORMONE condition, SEX and AGE, or from the "best" model if it was different and included AGE. Similarly for the *p*-value for EDUCATION also shown in Table 2.

Because there are 170 (5 × 34) *p*-values shown in Table 2, some type of multiplicity adjustment needed to be applied (i.e., the *p*-value threshold for statistical significance needed to be lower than the traditional 0.05). However, the relatively small sample size, and consequently low power, suggested allowing a higher *p*-value threshold. To account for these two factors that call for opposite *p*-value adjustments, the following informal rule was used:

- If $p>0.05$, the result is not statistically significant.
- If $0.01<p\leq0.05$, the result is considered statistically significant, but is preliminary and needs to be confirmed with further research.
- If $p\leq0.01$, the result is statistically significant.

A secondary analyses evaluated potential confounds in the data. First, during GnRH agonist-induced hypogonadism, plasma testosterone levels remained higher in men compared with women. Thus, to better match men and women for possible effects of testosterone on performance, we repeated the ANOVA-R between women and men who had total testosterone levels <50 ng/dl during hypogonadism in each cognitive task domain.

3. Results

Thirty one participants, 15 women [mean (SD) age = 33.9 (6.1) years] and 16 men [mean (SD) age = 27.0 (4.5) years] completed the study. Baseline group differences included age and education: men were younger ($p = 0.001$) and had more years of education ($p = 0.014$) than women. Women and men completed an average of 16.3 (2.0) and 17.7 (1.5) years of education, respectively. Mean WRAT-R scores did not differ between women and men ($p = 0.89$) (Table 1).

3.1. Effects of sex on cognitive task performance

We observed significant main effects of sex on several measures of visuospatial ability (Table 2). Men performed better than women on the mental rotation task (MRT), which was only reflected in the adjusted ($p = 0.002$) but not the raw scores. A similar significant effect of sex was observed in the completion of the Rey figure task, with men performing better than women on both the immediate ($p = 0.014$) and the delayed ($p = 0.023$) recall of the drawing. A main effect of sex also was observed (with men performing better than women) on the completion of the 15-item paired score of the Line Orientation ($p = 0.002$) task, the Porteus Maze [immediate] ($p = 0.005$), the Money Road Map (MRM) (time-up ($p = 0.007$); time total ($p = 0.023$); errors down ($p = 0.006$)), and Embedded Figures [best] ($p = 0.020$). An effect of hormone condition was also observed in several of these visuospatial tasks including: MRT [adjusted] ($p = 0.013$), MRM (time up ($p = 0.045$); time total ($p = 0.019$)), and Porteus Maze [immediate] ($p = 0.017$), reflecting improved performance in all of these measures during the second testing (i.e., hypogonadism) compared with baseline (eugonadal).

A significant sex by hormone condition interaction also was present in the performance of the Rey Figure task [delay] ($p = 0.047$), which reflected a worsening performance in women and an improved performance in men during the second testing compared with baseline. There were no significant interactive effects of sex by hormone condition in any of the other visuospatial tasks. Finally, we observed a significant effect of hormone condition ($p = 0.04$) but not sex ($p = 0.142$) in the performance scores of the unadjusted MRT reflecting a slight improvement in performance between the second and first testing sessions. Significant effects of age were observed in the performance of both the Rey Figure [delay] ($p = 0.022$) and the MRT [unadjusted] ($p = 0.030$) suggesting a significant linear relationship between age and performance after taking into account sex and hormone effects (i.e., in general, the older the person, the lower the score). A significant effect of education was also observed in the performance of the Porteus maze [delay] ($p = 0.027$) (i.e., the higher the education, the better the score).

A similar pattern of sex differences in visuospatial ability was obtained when test scores were re-analyzed in women ($N = 15$) and men ($N = 15$) with plasma testosterone levels <50 ng/dl during the hypogonadal state ($p<0.05$, Table 3) (data from one man whose plasma testosterone levels during hypogonadism were >50 ng/dl was excluded from this analysis). Plasma testosterone (mean(SD)) levels during hypogonadism in this new group were as follows: women = 21.2 (8.5) ng/dl and men = 13.6 (5.3) ng/dl.

In verbal memory, performance scores in men were significantly better than those in women on the paragraph memory [immediate] ($p = 0.042$) and the Digit Span ($p = 0.026$) tasks. Additionally, there was an effect of hormone condition in the paragraph memory [delay] ($p = 0.002$) and the Purdue Peg Board [dominant] ($p = 0.037$) tasks but no main effect of sex in either ($p = 0.53$ and 0.36, respectively). In paragraph memory scores [delay] there was a significant effect of education ($p = 0.021$) suggesting that education was associated with performance score, after taking into account treatment and sex effects (i.e., the higher the education, the higher the score).

For Symbol Digit [written], education was not statistically significant ($p = 0.581$) but the hormone condition-by-education interaction was statistically significant ($p = 0.0021$, p-value not shown in Table 2). The model parameter estimates indicate that at baseline, higher education was associated with higher scores; and after taking Lupron, higher education was associated with lower score. Although each association was not statistically significant, the fact that they were in opposite directions led to a statistically significant hormone condition-by-education interaction. We observed no other significant effects of sex, hormone condition, or sex by hormone condition interactions on task performance (including the performance on other tests of verbal memory, verbal fluency and articulation, motor speed and dexterity, and attention and concentration ($p>0.05$, all comparisons)).

3.2. Effects of GnRH agonist on mood and behavioral symptoms

No differences in BDI scores were present at baseline, nor were significant changes observed across hormonal conditions in either women or men (p = ns) (Table 3). Clinically significant day or night hot-flushes (i.e., seven-day average score ≥ 2) were reported by all women ($N = 14$) and seventy-three percent of men ($N = 11$) during hypogonadism (as well as vaginal dryness in women and decreased libido in some women and men (Schmidt et al., 2009)). None of the women or men reported day or night hot-flushes at baseline. Otherwise consistent with previous reports in these samples of healthy volunteers, Lupron administration was tolerated without the onset of significant mood or behavioral symptoms (Ben Dor et al., 2013; Schmidt et al., 2013; Schmidt et al., 2009). Plasma sex steroid levels during GnRH agonist-induced hypogonadism were consistently suppressed at the time of testing in all men and women relative to baseline conditions.

4. Discussion

Our findings replicate the observed male advantage in visuospatial performance and represent the first report of sex differences in visuospatial ability between adult women and men under conditions of induced hypogonadism. In particular, performance scores on the adjusted MRT, one of the most widely replicated sex differences in cognitive performance, were comparable to those reported previously, and differences in performance were maintained across both hormone conditions. Thus, the direction and magnitude of the sex difference we observed persisted in the absence of the marked differences in sex steroid levels seen between men and women under the usual physiologic study conditions. In contrast, with the exception of paragraph memory [immediate] scores, no significant sex differences were observed in the performances on the other cognitive domains measured (i.e., attention, concentration, and motor speed and dexterity). Finally, in contrast to some

reports in the literature (Cherrier et al., 2003; Grigorova et al., 2006), our findings also show that induced hypogonadism has few detrimental (Hier and Crowley, 1982) effects on visuospatial performance in either women or men, suggesting that, at least in the short term, the relative absence of circulating sex steroids does not impair visuospatial task performance in women or men.

The magnitude of the sex difference in MRT performance was comparable to that reported in several previous studies in which men and women were tested during eugonadal conditions (Voyer et al., 1995). Indeed, the effect size (Cohen's d; (Cohen, 1977)) in the observed difference between men and women in the MRT scores (unadjusted for age or education) was large (0.98), and was similar in magnitude to those observed in previous reports of the male advantage on the MRT performance (Kimura, 1987; Hampson, 1995; Linn & Petersen, 1985; Voyer et al., 1995). These effect sizes also extended to other measures of visuospatial function that we analyzed, including the Rey Figure [delay], Line Orientation, and Money Road Map [time in seconds up] (d = 1.2, d = 1.1, and d = 0.79, respectively).

Sex differences in performance also were maintained when we re-analyzed performance scores in groups of men and women matched for plasma testosterone levels (<50 ng/dl) during hypogonadism. Thus higher circulating testosterone levels in some hypogonadal men did not appear to contribute to the observed sex differences in visuospatial performance. Albeit possible that prolonged exposure to differing hormone levels throughout adulthood could have a larger impact on visuospatial performance than our short term hormone manipulation. Despite the demonstration of sex differences in visuospatial ability consistently across all measures administered, we observed significant effects of hormone condition in only three tests. These effects of hormone condition reflected improved performances in both women and men and likely were influenced by practice effects.

In women, our findings are consistent with studies that observed no difference in women's performance on visuospatial tasks across different phases of the menstrual cycle (Rosenberg and Park, 2002; Gordon and Lee, 1993) but contrast with other studies that showed improved visuospatial task performance accompanying elevated plasma levels of estradiol (Hausmann et al., 2000; Hampson, 1995; Hampson et al., 2014). Some studies report improved performance on visuospatial tasks (i.e., MRT) during low estradiol states (Simic and Santini, 2012) whereas others report either improved spatial abilities under conditions of elevated testosterone (Hausmann et al., 2000) or no differences in performance on the MRT during high estradiol states compared with low estradiol states (Maki et al., 2002). These ostensibly inconsistent findings might reflect the impact of a range of contextual factors that potentially influence the effects of sex steroids on cognitive performance in individual women including age, concurrent medical/gynecologic conditions, and the presence of multiple hormones with neuroactive potential during testing conditions. Similarly, in healthy men, studies report that conditions of high circulating testosterone are accompanied by increased (Thilers et al., 2006), decreased (Cherrier et al., 2007), or no change (Cherrier et al., 2002) in MRT performance scores and spatial ability.

In men, our findings contrast with several prior reports that testosterone replacement is associated with improved performance on visuospatial tests in hypogonadal men (Klaiber et al., 1971; Janowsky et al., 1994; Moffat et al., 2002). However, in some of these studies (Cherrier et al., 2003; Cherrier et al., 2005) the men were older and were being treated for an underlying medical condition (i.e., ADT for prostate cancer). Thus an older age or medical illness also could increase the impact of low testosterone levels in some men, consistent with findings by Young et al. who observed an effect of age on the correlation between plasma free testosterone levels and visuospatial tasks, with older but not younger men's performance showing a correlation with free testosterone (Young et al., 2010). Additionally, two studies reported associations between lower testosterone levels in men and improved performance on mental rotation tests (Gouchie and Kimura, 1991; Hier and Crowley, 1982), suggesting that either plasma testosterone levels do not substantially impact visuospatial performance or that an optimal level of testosterone is associated with an enhanced visual spatial performance (with higher levels and lower levels associated with poorer performance in men (Moffat and Hampson, 1996)).

Previous studies demonstrate the beneficial effects of estrogen therapy in older hypogonadal (post-menopausal) women on measures of verbal and visual memory in some (Kampen and Sherwin, 1994; Resnick et al., 1997; Joffe et al., 2006; Maki et al., 2001) but not all studies (Berman et al., 1997; Shaywitz et al., 1999; LeBlanc et al., 2001; Keenan et al., 2001). Additionally, several reports examined the effects of hypogonadism on cognitive performance in younger women receiving GnRH agonists for uterine fibroids or endometriosis (Sherwin and Tulandi, 1996; Grigorova et al., 2006), and in contrast to our data, the majority of these studies (Palomba et al., 2004; Craig et al., 2008a; Craig et al., 2008b; Craig et al., 2007; Varney et al., 1993) observed a significant decline in performance scores in measures of verbal memory, working memory, and visual recognition during hypogonadism compared with baseline. We were unable to identify significant declines in performance scores in tests of attention or verbal or visual memory during hypogonadism in this study. However, our findings are consistent with those of Owens (Owens et al., 2002), who also studied asymptomatic healthy women at baseline and after four months of GnRH agonist-induced ovarian suppression. These ostensibly discrepant findings could reflect clinically important differences in the characteristics of these women (i.e., older women or the presence of gynecologic illness) that could predict a differential response in cognitive function after either the natural or induced menopause-similar to reports of a differential mood response to declining estradiol secretion (Schmidt et al., 2015) in some women. Finally, the duration of hypogonadism in postmenopausal women would be considerably longer than in our study and may be associated with a differing responsivity to estrogen (Tinkler et al., 2002).

The presence of hot-flushes during hypogonadism has been suggested to influence the performance on a range of cognitive tests (Maki et al., 2008). In this study, as well as in a larger companion study in women only, we observed that hot-flushes had no significant effect on the performance of any of the cognitive tests administered (Schmidt et al., 2013). The majority of both women and men in this study experienced hot-flushes during the hypogonadal phase (100% and 73% respectively). Nonetheless, the presence of hot-flushes in our sample could not explain the identical pattern of sex-related performance differences

at baseline (i.e., during the eugonadal state) when hot-flushes were absent in both men and women and their similar performance during hypogonadism. The absence of an effect of hot-flushes on cognitive performance in several domains in women also was reported by Owens et al., in which young healthy women, with no comorbid medical diagnoses, underwent cognitive testing during ovarian hormone suppression (Owens et al., 2002). Similarly, Young et al. did not find the presence of hot-flushes during hypogonadism to adversely affect cognition in healthy older or younger men (Young et al., 2010). Nonetheless, it is possible that our study was not of sufficient duration to identify the longer-term effects of hot-flushes and the accompanying sleep disturbance on cognitive function in the tasks we measured. Similarly, in healthy volunteers, studies report only minor changes in mood or behavior in men and women (Ben Dor et al., 2013; Schmidt et al., 2013; Schmidt et al., 2009) receiving Lupron. Thus, we did not observe nor did we anticipate that the emergence of adverse mood symptoms would significantly impact cognitive performance in the participants of this study. However, our findings demonstrate that, in young, healthy women and men, neither short-term gonadal suppression nor the accompanying experience of hot-flushes result in an acute decline in cognitive performance.

Additional limitations of our study include multiple comparisons, small sample size, study duration, and order effects. Of the multiple comparisons made in this study, one can expect about 5% of test results to show statistical significance by chance. To account for multiple comparisons, we consider findings with *p*-values between 0.01 and 0.05 to be preliminary that need to be confirmed with further research. In this context, our findings of sex differences in visuospatial performance that endure across hormonal states suggest the robustness of this observation. Multiple visuospatial test scores met significance levels below $p = 0.01$, in the absence of comparably robust sex differences in other domains of cognitive function (or in the effects of induced hypogonadism relative to baseline). Indeed, sex differences in four of the tests in visuospatial performance were significant at the $p = 0.01$ level, whereas none of the effects of hormone condition or sex by hormone condition interactions in visuospatial measures met this level of statistical significance. Certainly, it is possible that several of the observed trends for sex differences in visuospatial performance (i.e., Embedded Figures [all] and Porteus Maze [delay], ($0.05<p<0.1$ for both) could reflect a type II error. In support of this possibility, the direction of these sex differences was consistent with the literature (and the performance scores on the MRT). It is also possible that, had we tested cognitive performance after a longer period of hypogonadism, we may have seen differences in task performance (i.e., declines in performance in both women and men). The performance on several test measures showed a slight nonsignificant improvement from baseline to hypogonadism in both men and women. Unfortunately, our fixed order study design does not permit the disambiguation of the effects of practice (due to repeated testing) and the hormone conditions induced. Nonetheless, in previous reports in women, a similar pattern of improvement related to repeated testing appeared independent of hormone condition (Schmidt et al., 2013; Owens et al., 2002). It is also possible that an effect of order may explain why performance scores somewhat improved with the second task administration (during hypogonadism) though the male advantage in visuospatial task performance remained consistent. Thus, although practice effects may have obscured adverse effects of drug, the scores between baseline and Lupron treatment were slightly but

insignificantly higher, consistent with a small practice effect. Additionally, administration of the same battery at the same time points to un-medicated men (unpublished data) and women (Schmidt et al., 2013) revealed no practice effects between time 1 and time 2 in the vast majority of visuospatial measures employed in this study. Finally, women and men differed with respect to age and education, and in several test scores these effects remained significant after accounting for sex and hormone effects.

A recent population-based study (Ganguli et al., 2010) reported that age and education (combined) accounted for only 9% of the variance in visuospatial performance scores. Nevertheless, a more carefully matched sample could have avoided this potential confound. In particular, age or education probably contributed to the observed sex difference in the verbal memory task [immediate] in which, paradoxically, men performed better than women. This finding stands in contrast to literature documenting women's advantage in verbal memory (Caselli et al., 2015). Our finding, which was marginally significant, likely reflects the effects of the small sample size and differences in education between men and women rather than a true male advantage in verbal memory.

There are several possible explanations for our findings. The persistence of sex differences during induced hypogonadism suggests that these differences in visuospatial abilities between women and men do not reflect the presence of sex differences in circulating sex steroids in the adult men and women participating in this study. These differences in cognitive task performance might better reflect the sex-specific differences in early organizational effects of sex steroids or the effects of sex-specific developmental factors (social/environmental cuing) in childhood. Indeed, the possibility that sex differences in visuospatial ability could reflect earlier (in utero) effects of differing sex steroid milieus is supported by some reports of sex differences in visuospatial abilities in prepubertal boys and girls who would not be exposed to the circulating levels of sex steroids of adulthood (Newhouses et al., 2007; Heil et al., 2011). However, in one study that compared visuospatial skills in prepubertal boys and girls with their levels of fetal testosterone (obtained from second trimester amniotic fluid 710 years prior) did not correlate with MRT performance in childhood (Auyeung et al., 2012). Alternately, differing performances between men and women on visuospatial abilities could reflect sex differences in developmental exposures in education and recreational activities as well as sex differences in social cuing experienced during childhood (McCarthy and Konkle, 2005).

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Table 1

Baseline characteristics of women (n = 15) and men (n = 16) before treatment with Lupron. Data reported as mean (SD) unless otherwise indicated.

Variable	Women	Men	test (df), (p-value)
Age (years)	33.9(6.1)	27.0(4.5)	t(29) = 3.6(0.001)
Education (number of years)	16.3(2.0)	17.7(1.5)	t(29) = −2.6(0.014)
Handedness (N right-handed)	13	16	$\chi^2(1) = 2.3,(0.13)$
WRAT-R*	114.3(6.9)	114.1(3.4)	t(19) = 0.13,(0.89)
Menstrual cycle phase at baseline testing**			
Follicular (days 211) [N]	7		
Luteal (days 1828) [N]	8		

*Women and men were matched for IQ; all scores ranged between 100 and 125.

**All women reported regular, 2830 day menstrual cycles.

Table 2

Cognitive performance test scores in women (W) and men (M) at baseline (when eugonadal) and after 68 weeks of Lupron administration (when hypogonadal). Data are represented as least squares (LS) means (SE).*

Task	Sex	Baseline	Lupron		*p*-value	Effect Size	SE	(LCL,UCL)	Sex x Treatment *p*-value	Age *p*-value	Education *p*-value
Memory											
Rey Complex Figures (visual)-Copy (score)	W	35.2 (0.22)	35.5 (0.14)	Hormone effect	0.260	0.13	0.12	(−0.10,0.37)	0.260	0.788	0.298
	M	35.9 (0.22)	35.9 (0.13)	Sex effect	0.014	0.60	0.23	(0.13,1.08)			
Rey Complex Figures (visual)-Delay (score)	W	23.2 (1.3)	21.4 (1.3)	Hormone effect	0.927	0.08	0.91	(−1.77,1.94)	0.047	0.022	0.320
	M	25.4 (1.2)	27.4 (1.2)	Sex effect	0.023	4.05	1.69	(0.60,7.51)			
Paragraph Memory (verbal)-Immediate (% paragraph)	W	56.4 (3.9)	66.2 (3.9)	Hormone effect	0.088	5.43	3.08	(−0.86,11.73)	0.167	0.608	0.068
	M	70.4 (3.8)	71.4 (3.8)	Sex effect	0.042	9.61	4.50	(0.40,18.82)			
Paragraph Memory (verbal)-Delay (% paragraph)	W	50.1 (4.1)	63.7 (4.1)	Hormone effect	0.002	10.49	3.07	(4.21,16.77)	0.309	0.666	0.021
	M	56.5 (4.0)	63.8 (4.0)	Sex effect	0.528	3.22	5.05	(−7.12,13.57)			
Spatial ability											
Line Orientation-15-item (paired score)	W	12.7 (0.5)	12.6 (0.5)	Hormone effect	0.764	−0.10	0.34	(−0.80,0.59)	0.906	0.528	0.639
	M	14.6 (0.4)	14.5 (0.4)	Sex effect	0.002	1.89	0.54	(0.78,3.00)			
Line Orientation-30-item (total score)	W	27.6 (1.1)	27.5 (0.6)	Hormone effect	0.962	0.02	0.47	(−0.94,0.98)	0.727	0.127	0.282
	M	28.1 (1.0)	28.3 (0.6)	Sex effect	0.580	0.65	1.16	(−1.72,3.02)			
Mental Rotation-Total (Number correct)	W	13.6 (1.2)	13.8 (1.2)	Hormone effect	0.040	1.53	0.71	(0.08,3.00)	0.086	0.030	0.483
	M	14.9 (1.2)	17.7 (1.2)	Sex effect	0.142	2.57	1.70	(−0.91,6.05)			
Mental Rotation-Adjusted (Number correct)	W	8.4 (1.4)	9.2 (1.4)	Hormone effect	0.013	2.13	0.81	(0.48,3.79)	0.110	-	0.225
	M	13.5 (1.4)	16.9 (1.4)	Sex effect	0.002	6.40	1.86	(2.59,10.21)			
Embedded Figures-Best (seconds)	W	18.5 (2.3)	15.1 (1.6)	Hormone effect	0.068	−2.81	1.48	(−5.84,0.22)	0.711	0.583	0.491
	M	12.3 (2.2)	10.0 (1.5)	Sex effect	0.020	−5.63	2.28	(−10.3,−0.96)			
Embedded Figures-All (seconds)	W	23.8 (3.2)	24.8 (3.2)	Hormone effect	0.768	0.84	2.82	(−4.92,6.60)	0.947	0.476	0.360
	M	17.0 (3.1)	17.7 (3.1)	Sex effect	0.059	−6.95	3.53	(−14.17,0.28)			
Money Road Map-Time up (seconds)	W	24.5 (2.3)	21.1 (1.4)	Hormone effect	0.045	−2.23	1.07	(−4.41,−0.05)	0.257	0.426	0.170
	M	16.3 (2.2)	15.3 (1.3)	Sex effect	0.007	−7.05	2.41	(−11.98,−2.12)			
Money Road Map-Time total (seconds)	W	62.9 (5.2)	52.6 (5.2)	Hormone effect	0.019	−6.01	2.42	(−10.97,−1.05)	0.090	0.915	0.718
	M	42.2 (5.1)	40.4 (5.1)	Sex effect	0.023	−16.42	6.85	(−30.42,−2.42)			
Money Road Map-Errors up (Number)	W	0.33 (0.16)	0.53 (0.16)	Hormone effect	0.613	0.07	0.13	(−0.21,0.34)	0.337	0.388	0.225

Task	Sex	Baseline	Lupron		*p*-value	Effect Size	SE	(LCL,UCL)	Sex x Treatment *p*-value	Age *p*-value	Education *p*-value
	M	0.19 (0.16)	0.13 (0.16)	Sex effect	0.147	−0.28	0.19	(−0.66,0.10)			
Money Road Map-Errors down (Number)	W	1.20 (0.29)	1.27 (0.29)	Hormone effect	0.364	−0.22	0.23	(−0.70,0.26)	0.237	0.867	0.126
	M	0.50 (0.28)	0.00 (0.28)	Sex effect	0.006	−0.98	0.33	(−1.66,−0.30)			
Porteus Maze-Immediate (seconds)	W	55.1 (6.3)	40.9 (3.2)	Hormone effect	0.017	−11.57	4.58	(−20.9,−2.2)	0.570	0.701	0.082
	M	36.6 (6.1)	27.7 (3.1)	Sex effect	0.005	−15.81	5.20	(−26.4,−5.2)			
Porteus Maze-Immediate (Number errors)	W	1.53 (0.37)	1.67 (0.37)	Hormone effect	0.989	0.00	0.29	(−0.58,0.59)	0.657	0.142	0.486
	M	1.38 (0.36)	1.25 (0.36)	Sex effect	0.503	−0.29	0.42	(−1.15,0.58)			
Porteus Maze-Delay (seconds)	W	32.7 (4.7)	32.7 (4.7)	Hormone effect	0.827	−0.47	2.12	(−4.81,3.87)	0.827	0.802	0.027
	M	22.9 (4.5)	22.0 (4.5)	Sex effect	0.127	−10.19	6.48	(−23.47,3.09)			
Porteus Maze-Delay (Number errors)	W	1.00 (0.26)	1.13 (0.26)	Hormone effect	0.446	−0.12	0.16	(−0.44,0.20)	0.115	0.745	0.685
	M	0.69 (0.25)	0.31 (0.25)	Sex effect	0.086	−0.57	0.32	(−1.22,0.09)			
Verbal fluency											
Verbal Fluency-Number of words generated	W	40.1 (2.3)	43.3 (2.3)	Hormone effect	0.086	2.29	1.29	(−0.34,4.92)	0.484	0.223	0.340
	M	44.9 (2.2)	46.3 (2.2)	Sex effect	0.197	3.83	2.90	(−2.10,9.76)			
Stroop Color Naming-Number of words read	W	51.1 (1.7)	50.6 (1.7)	Hormone effect	0.566	0.30	0.51	(−0.75,1.35)	0.147	0.885	0.830
	M	50.8 (1.7)	51.9 (1.7)	Sex effect	0.829	0.51	2.35	(−4.29,5.31)			
Motor speed/dexterity											
Purdue Peg Board-Dominant (Number pegs)	W	14.7 (0.3)	15.1 (0.3)	Hormone effect	0.037	0.61	0.28	(0.04,1.17)	0.464	0.410	0.582
	M	14.1 (0.3)	14.9 (0.3)	Sex effect	0.358	−0.34	0.36	(−1.07,0.40)			
Purdue Peg Board-Non-dominant (Number pegs)	W	14.3 (0.4)	13.9 (0.4)	Hormone effect	0.661	−0.10	0.24	(−0.59,0.38)	0.338	0.687	0.069
	M	13.9 (0.4)	14.1 (0.4)	Sex effect	0.844	−0.10	0.50	(−1.13,0.93)			
Purdue Peg Board-Both hands (Number pegs)	W	11.7 (0.3)	12.0 (0.3)	Hormone effect	0.543	0.13	0.22	(−0.31,0.58)	0.543	0.664	0.070
	M	11.3 (0.3)	11.3 (0.3)	Sex Effect	0.156	−0.55	0.38	(−1.33,0.22)			
Purdue Peg Board-Assembly (Number pegs)	W	18.7 (0.8)	18.6 (0.8)	Hormone Effect	0.980	−0.01	0.43	(−0.89,0.87)	0.866	0.374	0.272
	M	19.5 (0.7)	19.6 (0.7)	Sex Effect	0.357	0.91	0.97	(−1.07,2.89)			
Grooved Pegboard-Dominant (seconds)	W	56.1 (1.9)	57.4 (1.9)	Hormone Effect	0.797	0.28	1.09	(−1.94,2.51)	0.342	0.140	0.861
	M	55.4 (1.8)	54.7 (1.8)	Sex Effect	0.482	−1.68	2.36	(−6.51,3.15)			
Grooved Pegboard-Non-dominant (seconds)	W	57.9 (2.2)	57.0 (2.2)	Hormone Effect	0.575	0.60	1.06	(−1.57,2.77)	0.158	0.297	0.219
	M	53.0 (2.2)	55.1 (2.2)	Sex Effect	0.258	−3.41	2.95	(−9.45,2.63)			
Finger Tapping-Dominant (Number taps)	W	54.8 (1.6)	55.8 (1.6)	Hormone Effect	0.125	1.33	0.84	(−0.40,3.06)	0.679	0.143	0.173
	M	57.4 (1.6)	59.1 (1.6)	Sex Effect	0.167	2.99	2.10	(−1.33,7.31)			

Task	Sex	Baseline	Lupron		*p*-value	Effect Size	SE	(LCL,UCL)	Sex x Treatment *p*-value	Age *p*-value	Education *p*-value
Finger Tapping-Non-dominant (Number taps)	W	50.9 (1.5)	51.1 (1.5)	Hormone Effect	0.970	0.03	0.73	(−1.46,1.52)	0.793	0.072	0.937
	M	50.1 (1.5)	50.0 (1.5)	Sex Effect	0.639	−0.95	2.00	(−5.06,3.16)			
Attention/Concentration											
Digit Span-Correct response (Number back)	W	5.5 (0.3)	5.9 (0.3)	Hormone Effect	0.459	0.16	0.21	(−0.28,0.60)	0.274	0.781	0.502
	M	6.6 (0.3)	6.5 (0.3)	Sex Effect	0.026	0.81	0.34	(0.10,1.51)			
Symbol Digit-Written (Number correct)	W	59.6 (2.0)	56.3 (2.0)	Hormone Effect	0.113	−1.38	0.84	(−3.10,0.35)	0.047	0.539	0.581
	M	58.8 (1.9)	59.4 (2.0)	Sex Effect	0.676	1.17	2.78	(−4.52,6.86)			
Symbol Digit-Oral (Number correct)	W	73.1 (2.8)	70.3 (2.8)	Hormone Effect	0.214	−2.06	1.62	(−5.38,1.26)	0.622	0.339	0.742
	M	73.4 (2.7)	72.2 (2.7)	Sex Effect	0.752	1.11	3.48	(−6.01,8.24)			
Symbol Digit-Recall (Number correct)	W	7.5 (0.5)	7.8 (0.5)	Hormone Effect	0.516	0.22	0.33	(−0.46,0.90)	0.733	0.659	0.066
	M	8.2 (0.4)	8.3 (0.4)	Sex Effect	0.270	0.61	0.54	(−0.50,1.71)			
Trail Making-Form A (seconds)	W	21.1 (1.1)	19.8 (1.1)	Hormone Effect	0.416	−0.67	0.81	(−2.32,0.99)	0.416	0.852	0.714
	M	18.5 (1.1)	18.5 (1.1)	Sex Effect	0.152	−1.93	1.31	(−4.62,0.76)			
Trail Making-Form B (seconds)	W	45.8 (2.8)	42.9 (2.8)	Hormone Effect	0.285	−2.50	2.29	(−7.19,2.19)	0.874	0.917	0.936
	M	41.7 (2.8)	39.6 (2.8)	Sex Effect	0.257	−3.70	3.20	(−10.25,2.85)			

Hormone condition Effect=Lupron-Baseline. Sex Effect=Men-Women. SE=Standard Error of the Mean. LCL=Lower limit of 95% confidence interval. UCL=Upper limit of 95% confidence interval. =Not considered.

Table 3

Plasma hormone levels, mood symptoms, and hot flushes in women and men before and after Lupron administration. Data are reported as mean (SD) unless otherwise indicated.

	Women [*n* = 15]	**Men [*n* = 16]**
Estradiol (pg/ml)		
Baseline	100.8 (74.2)	25.0 (9.6)
Hypogonadal	14.4 (4.9)	3.9 (1.1)
Progesterone (ng/ml)		
Baseline	3.7 (4.9)	*a*
Hypogonadal	0.4 (0.1)	*a*
Testosterone (ng/dl)		
Baseline	*a*	475.2 (174.2)
Hypogonadal	21.2 (8.5)	18.8 (21.5)
BDI[b]		
Baseline	1.4 (1.3)	0.8 (1.1)
Hypogonadal	3.6 (5.5)	2.9 (3.8)
Hot-Flushes Number of subjects (%)		
Baseline	None	None
Hypogonadal	15 (100%)	11 (73.3%)

Plasma hormone level conversions are as follows: Estradiol: pg/ml × 3.67 = pmol/L; Progesterone: ng/ml × 3.18 = nmol/L; and Total testosterone: ng/dl x.0347 = nmol/l.

[a] Plasma hormone levels not measured.

[b] The BDI is a 21 item self-administered scale with a maximum score of 63 (higher scores represent more severe depressive symptoms).