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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 6–8 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 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.
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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

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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 preclinical 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 6–8 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 6–8 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