Spatial Cognition in Humans: Possible Modulation by Androgens and Estrogens

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Many studies in nonhuman species have shown that gonadal steroid hormones can influence the regional structure and physiology of the central nervous system, and can bring about both short- and long-term effects on behavior. The extent to which human behavior and thought processes are subtly influenced by the hormonal milieu is unclear. There is preliminary evidence from a number of clinical endocrine syndromes, and from studies of normal human subjects, that sex steroids may modulate the expression of certain specific cognitive abilities. This paper will briefly review some recent evidence suggesting that visual-spatial abilities are among the cognitive functions that may be affected.

Key Words: spatial ability, cognitive abilities, androgen, estrogen, human

INTRODUCTION

In the past 25 years, research from a variety of mammalian species has suggested that the steroid hormones secreted by the gonads (e.g., testosterone, 17-β-estradiol) may play a variety of regulatory roles in the central nervous system. During fetal or neonatal brain development, sex steroids appear to play a fine-tuning function in certain regions of the brain, modifying events related to neuronal survival and synapse formation (Breedlove 1992). In the adult brain, sex steroids are capable of modulating synaptic transmission or neurosecretion in numerous hypothalamic and extra-hypothalamic brain areas by interacting with specific nuclear or membrane receptors. They may also retain some growth-promoting properties (McEwen 1991; Schumacher 1990; Woolley and McEwen 1992).

It is reasonable to expect that these brain-related events have some functional or behavioral consequences. Indeed, both permanent (organizational) and reversible (activational) effects of sex steroids on behavior have been identified (Arnold and Breedlove 1985). Among the behaviors in non-human vertebrates that have been shown experimentally to be hormone-sensitive are mating or reproductive behaviors, maternal behaviors, territorial behaviors (including bird-song), aggression, taste preferences, and certain motor behaviors (Becker and others 1992).

Perhaps one of the most surprising aspects of behavior that can be modified by sex steroids in nonhuman species is spatial-navigational behavior. This refers to an animal's ability to navigate accurately in 3-dimensional space, and to learn and use routes to reach targets or goals efficiently. In a number of species, this is a sexually differentiated function, in that male animals more readily learn spatial-navigational tasks than do females (Beatty 1984). In the evolutionary sense, this sexual dimorphism has been hypothesized to relate to mating strategies (Gaulin and Fitzgerald 1986) or other aspects of the reproductive ecology of a species (Greenwood 1980).

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In rodents, spatial behavior is studied in the laboratory by examining an animal's ability to navigate or learn the layout of spatial mazes such as the radial arm maze or Morris water maze. Such tasks have revealed that sex steroids exert both organizational and activational influences on maze performance. Administration of either testosterone propionate (Roof and Havens 1992) or estradiol benzoate (Williams and others 1990) to female rats in the neonatal period results in improved spatial maze performance in adulthood. Neonatal castration of male rats reduces adult spatial proficiency, compared with male controls. Neonatal hormone manipulations may differentially alter reliance on different types of visual cues used in spatial problem-solving (Williams and others 1990). There is also preliminary evidence of activational effects of androgens and estrogens in reproductive adults. For example, estrous-cycle dependent variation in radial maze performance has been reported in the rat, with females displaying more errors at proestrus (Sauve and others 1990). Female rats have also been reported to exhibit poorer performance in the Morris water maze when tested at high levels of circulating estrogens (Korol and others 1994). At least 2 other studies, however, which did not use a naturalistic manipulation of hormone levels, did not find such effects (Luine and Rodriguez 1994; Williams 1995). In deer mice, spatial learning proficiency varies in both sexes with the breeding season (Galea and others 1994). In the meadow vole, higher levels of circulating estradiol are correlated with poorer learning and retention of a spatial maze task (Galea and others 1995).

Spatial abilities in humans are of several distinct types (Hampson and Kimura 1992) and display a degree of sexual differentiation. Although there is substantial overlap in the distributions of scores, males tend on average to perform better than females on many spatial tasks. These include route-learning tasks and also paper-and-pencil tests in which subjects must mentally transform, manipulate, or rotate stimuli, or imagine what visual stimuli would look like when seen from alternate orientations. Simple perceptual matching (i.e., determining whether 2 visual stimuli are identical in all features) is not a spatial ability since no dynamic transformation of the stimulus is required in solving the task. The sex difference on spatial tests ranges from about 0.25 to about 1.0 standard deviation in size, although sex differences as large as the latter are typically found only on very difficult spatial tests such as the Vandenberg Mental Rotation Test (Vandenberg and Kuse 1978). There may also be spatial abilities that show the contrary sex difference in favor of females (Silverman and Eals 1992), although these have not been studied extensively, and there is some debate about whether they actually constitute spatial abilities by formal definitions.

To date, neuroendocrine research in other species suggests that it is sexually dimorphic behaviors which are most subject to hormonal influence. Because human spatial abilities show some sexual differentiation, and because related abilities in non-human mammals appear to be hormone-sensitive, it is reasonable to ask whether spatial abilities in humans are also subject to organizational and/or activational influences of sex steroids.

It should be noted that the range of spatial behaviors assessed to date in rodent species is very limited, restricted almost exclusively to spatial-navigational behaviors. No suitable animal model currently exists for many of the spatial functions routinely assessed in humans such as mental rotation. Although some of these complex spatial skills have been shown empirically to share variance in common with route-learning tasks in humans (Galea and Kimura 1993), it is not obvious how they relate to the available nonhuman data. It is often tacitly assumed by researchers that data based on spatial-navigational tasks in rodents are directly relevant to our understanding of a range of spatial abilities in humans, but great caution in making such an inference seems warranted since these tasks have very diverse information-processing demands, and comparability in the underlying neurobiology has not been demonstrated.

Nevertheless, the possibility that sex steroids may influence spatial abilities in humans is supported by several indirect observations. For example, sex differences in spatial abilities are observed across many diverse cultures (Mann and others 1990), and are not fully accounted for by experiential or sociocultural factors (Baenninger and Newcombe 1989). Furthermore, differences between the sexes in spatial proficiency may not become fully expressed until around puberty (Maccoby and Jacklin 1974; for a different opinion, see Kerns and Berenbaum 1991). Although there has been little study of sex differences during the later part of the lifespan, a few studies suggest that the sex difference in spatial ability may be reduced in old age (Schwartz and Karp 1967). There is also preliminary evidence that spatial abilities are affected in several clinical endocrine syndromes that involve changes in sex steroid levels or receptivity (Hines 1982). Cumulatively, these observations suggest that androgens and/or estrogens may play some modulatory role in the expression of human spatial abilities.

Possible organizational effects of androgens on spatial abilities

In humans, it has yet to be established whether or not sex steroids, during prenatal development or in infancy, play any role in the differentiation of the developing brain. More specifically, it is an open question whether exposure to androgens or estrogens during early sensitive periods exerts any lasting influence on cortical or subcortical brain systems subserving higher-level mental processes and spatial abilities in particular. There are currently several pieces of indirect evidence, mainly from clinical research, suggesting that this may be so.

The first piece of evidence involves an endocrine condition called congenital adrenal hyperplasia (CAH). This is a disorder of the adrenal hormones that begins in the early prenatal period, and involves production of excessive levels of adrenal androgens. Once detected, usually shortly after

birth, medication can be instituted to normalize androgen concentrations. Thus, in early treated individuals, the androgen excess is limited to pre and early neonatal life. If there exists a critical period during prenatal development when fetal androgens normally help organize brain systems subserving spatial processes, then females who have CAH, because of their unusually high androgen exposure in utero, should show enhanced spatial abilities.

Resnick and others (1986) reported evidence consistent with this hypothesis. In a sample of adolescent and young adult subjects, females with CAH showed significantly better performance on several different tests of spatial ability than unaffected sibling controls. Importantly, this effect was limited to spatial tests; other tests measuring different cognitive functions showed no enhancement in Resnick's CAH sample, nor did the effects appear to be attributable to any differences in early childhood experiences. Another recent study was able to replicate and extend Resnick's findings in a preadolescent sample of children with CAH (Hampson and others 1994). Girls with CAH showed superior spatial performance compared with same-sex sibling controls on a test of spatial visualization, thus strengthening the case for an organizational effect of the hormone. The better performance of girls with CAH was again selective, and did not extend to other cognitive tests including tests of a nonspatial but pictorial nature.

The evidence from CAH is consistent with a recent study of dizygotic twins (Cole-Harding and others 1988), which found that females with a male twin displayed better spatial ability and more rapid learning on the Vandenberg Mental Rotations Test than females with a female twin. This difference was hypothesized to result from slightly raised androgens in the fetal hormone environment of the former, and is consistent with effects reported in some animal species (Williams and Meck 1991).

More paradoxical findings were reported by Finegan and others (1992). These investigators measured testosterone in second trimester amniotic fluid obtained by amniocentesis, and examined the relationship to a battery of cognitive measures in the normal singleton offspring of these pregnancies at age 4. On a block-building task, believed to measure spatial relations in this age group, girls with high average block-building scores had lower amniotic testosterone levels than girls with low average block-building scores, while boys showed a marginally significant trend in the opposite direction. This inconsistent pattern of results could be accounted for by a number of different factors including: 1. the timing of amniotic fluid collection, which may not have coincided with the hypothetical sensitive period for the differentiation of spatial functions; 2. the very young age at assessment of spatial ability in these children; or 3. the nature of the spatial task administered. In favor of the latter possibility is the fact that a recent reassessment of the same group of children at age 7 years, using a mental rotation task, revealed a positive correlation between prenatal testosterone and the rate of rotation in girls (Grimshaw and others, forthcoming).

Other clinical endocrine syndromes may prove to be important in evaluating the organizational hypothesis, but little work has been done in this context to date. A notable example is patients with isolated hypogonadotropic hypogonadism (IHH), which in some cases is associated with anosmia (Kallmann's syndrome). Despite a normal 46XY karyotype, males with this disorder have extremely low plasma testosterone levels secondary to a deficiency in GnRH (hypothalamic gonadotropin-releasing hormone). In at least 2 investigations, IHH males have been reported to manifest poorer performance than age-matched controls on spatial measures (Buchsbaum and Henkin 1980; Hier and Crowley 1982). Nonsignificant findings were reported by Cappa and others (1988). Of particular interest is the fact that males with IHH are believed to undergo relatively normal masculinization in utero under the influence of maternal gonadotropins. Therefore, if their spatial deficits are attributable to androgen deficiency during some critical period in brain development, as suggested in some studies (Hier and Crowley 1982), the IHH data could be quite important in implying that some organizational effects of androgens or their metabolites might occur postnatally, before or at puberty. To date, however, the possibility that developmental brain anomalies unrelated to hormone exposure may account for the spatial deficits in IHH has not been definitively ruled out. It should be noted that although Hier and Crowley (1982) did not find an ameliorative effect of androgen replacement therapy on spatial performance in IHH, sample size in this component of their study was exceedingly small. In light of other recent evidence for effects of exogenous androgens on spatial cognition (see below), the possibility that androgen replacement might attenuate the spatial deficit in IHH warrants further investigation, both from a theoretical and a clinical viewpoint.

The exclusive focus of most human studies on possible organizational effects of early androgens or their derivatives reflects the predominant view in the neuroendocrine literature that feminization of the female brain is a passive process that occurs automatically in the relative absence of androgens. There is increasing evidence, however, to suggest that ovarian hormones might play an active role in certain aspects of neural and behavioral organization (Hendricks 1992; Toran-Allerand 1991). In humans, females with the 45,X Turner's syndrome and its variants display a lifelong deficiency in ovarian steroid production as a result of gonadal dysgenesis. In many studies, girls with Turner's syndrome have been found to have spatial processing impairments compared with normal girls (Rovet and Netley 1982), along with other characteristics suggestive of atypical cognitive development (Waber 1979). It is widely assumed that the Turner fetus is steroid-deficient in utero (Hines 1982), but in fact this is not well substantiated (Lippe 1991). The most conservative interim assumption is that the spatial deficits in Turner's syndrome are most likely a reflection of alterations in brain development associated with the missing sex chromatin per se (Rovet and Netley 1982), but the possibility cannot be excluded that lack of gonadal steroids, possibly postnatally, also contributes to the pattern of deficits

observed. Notably, in most girls with Turner's syndrome, the postnatal elevation in estradiol, which normally occurs in the first year of life (Forest and others 1976) would presumably be absent.

Thus, although there is preliminary evidence in favor of an organizational effect of prenatal androgens on spatial functions, evidence for this in humans is indirect, and studies in this area are still too few to permit strong generalizations to be made. A more detailed review of this literature can be found in Hampson and Kimura (1992). Findings from clinical studies must be cautiously interpreted until the nature and limits of any effects on spatial functions are more fully understood.

Circulating androgens or estrogens and spatial performance in adults

Under ordinary circumstances, it is impossible, for ethical reasons, to manipulate gonadal hormones in normal people experimentally. This restriction places constraints on the types of studies that may be carried out in humans. In the past 10 years, most studies examining the relation between spatial abilities and circulating levels of gonadal steroids in adults have employed 1 of 3 approaches: 1. assessing spatial abilities in groups differing in mean hormone concentrations at time of testing; 2. examining correlations between individuals' scores on specific spatial tests and estimates of their level of circulating hormone at time of assessment, as determined through blood or salivary radioimmunoassays; or 3. employing direct administration of sex steroids, with or without a double-blind design. The latter are exceptional in this area of research, but provide the strongest evidence for activational effects of gonadal hormones.

The menstrual cycle provides a natural paradigm for studying the effects of physiological variations in ovarian steroids. In healthy women, serum concentrations of 17-β-estradiol range from 30 pg/mL to 50 pg/mL during menses to peak values which can be in excess of 300 pg/mL during the preovulatory surge in estradiol (Abraham 1978). After ovulation, estradiol concentrations reach a more gradual secondary peak of around 100 pg/mL to 150 pg/mL during the middle of the luteal phase. Progesterone concentrations also vary across the menstrual cycle, rising after ovulation to reach maximum concentrations during the midluteal phase. While there appears to be no relationship between either general cognitive competence or performance of routine everyday tasks, and phase of the menstrual cycle (Sommer 1992), there may be subtle fluctuations in spatial problem-solving capacity related to variations in ovarian hormone levels. It should be stressed that, in most women, these fluctuations are too small to be noticeable in everyday life (Hampson 1990b), but they can be detected in the laboratory when specialized spatial tests are used. Despite some inconsistency in findings, probably due to the small size of the effects and differences in methodology, many studies have now reported a slight diminution in spatial performance during the very high estrogen concentrations that characterize the midluteal and preovulatory phases, especially compared with women's performance during menses when levels of ovarian hormones are at their nadir (Broverman and others 1981; Hampson 1990a, 1990b; Hampson and Kimura 1988; Komnenich and others 1978; Silverman and Phillips 1993). Gordon and Lee, however, failed to find significant changes in spatial performance (1993). It must be emphasized that these effects are highly selective. In our own studies, for example, women's performance at the midluteal and preovulatory phases was actually improved, compared with their menstrual phase performance, on several manual and articulatory motor tasks used for comparison (Hampson and Kimura 1988), and, in one study, on tests of verbal fluency as well (Hampson 1990a). It is probably not a coincidence that tests of verbal fluency and fine motor skills often exhibit sex differences in favor of women (Maccoby and Jacklin 1974).

These effects have been found to show some dose dependency, making predictions difficult for other phases of the menstrual cycle differing less markedly in circulating ovarian hormone concentrations. Effects may also vary somewhat depending on the specific aspect of spatial ability measured. The Hampson study (1990b), for example, plotted the level of estradiol in serum (as determined by radioimmunoassay from blood sampling done just before or after cognitive testing), for a sample of 56 women tested throughout the follicular phase of the cycle, against each woman's performance on a test of spatial visualization, i.e., the Space Relations subtest from the Differential Aptitude battery. The relationship between circulating estradiol and accuracy on the Space Relations test was best approximated by an inverted U-shaped function. The degree of relationship was moderate in size, as one would expect, given that spatial performance is not determined exclusively by hormone levels, but is also influenced by a number of other biological and environmental variables (Casey and Brabeck 1989). Nevertheless, women displayed optimum performance on the Space Relations test at intermediate concentrations of estradiol, while very high estradiol concentrations were associated with reduced accuracy. Certain fine motor skills may also display a dose-dependent relationship to estrogen levels (Hampson 1991).

To summarize, several recent menstrual cycle studies suggest that transient variations in ovarian steroid concentrations are accompanied by variation in the expression of spatial abilities in women. Because repeated measure designs have been used in a number of these studies, and because these effects appear to be restricted to specific cognitive domains, general factors such as demographic features of the subjects, or affective or motivational changes, cannot adequately account for the observed associations. Mood changes are not typically seen on the days of the menstrual cycle being sampled in these studies, although Hampson (1990b) did observe a preovulatory enhancement in positive affect. This finding did not account for the slight diminution in spatial performance seen in this study at the preovulatory phase. A direct or indirect effect of gonadal hormones on brain systems

involved in spatial processing is postulated as the most likely explanation for these findings.

Other recent studies are relevant to the question of whether or not circulating testosterone levels have any implications for spatial processing capacities in men. Although studies on this topic are rare, several recent investigations that measured testosterone or other androgens in blood and/or saliva have reported significant associations between androgen levels and performance on various spatial tasks (Christiansen and Knussmann 1987; Gouchie and Kimura 1991; McKeever and Deyo 1990; Moffat 1993; Shute and others 1983). Nonsignificant results were reported by McKeever and others (1987). The findings as yet do not present a consistent picture, but a pattern emerging from several recent studies is that, in normal men, the highest levels of testosterone may be associated with lower spatial scores, at least on certain spatial tests, compared with men who have lower testosterone at the time of assessment. This pattern is reminiscent of earlier reports of a weak inverse association in men between indices of somatic androgenization and performance on spatial visualization tests (Klaiber and others 1967; Petersen 1976). In recent studies, when both sexes are considered jointly, thus expanding the range of physiologically possible testosterone values, there is evidence of a nonmonotonic relationship between androgen concentration and accuracy of spatial performance (Moffat 1993; Shute and others 1983). Two studies have found that, in women, the most accurate performance on spatial tests is seen in those with the highest androgen levels; and in young men, among those with the lowest androgen levels (Gouchie and Kimura 1991; Shute and others 1983), implying, tentatively, that within the total physiological range, optimal spatial functioning may be associated with intermediate concentrations of androgens. Until these findings are replicated, however, any firm conclusions about the form of the relationship between androgens and spatial abilities would be premature.

These preliminary studies are beginning to describe the form of the relationship between testosterone and spatial performance, but they provide little information about the reasons for the observed associations. The observed relationships could signify a dynamic effect of circulating hormones on brain systems subserving some aspect of spatial processing, but several other explanations for these findings are possible and not conclusively ruled out by existing data (Gouchie and Kimura 1991). The correlational methodology used in these studies simply does not permit any definitive conclusions to be drawn regarding possible causal roles of hormones in generating the observed associations.

Stronger evidence that circulating sex hormones may modulate the expression of spatial abilities in men comes from recent work employing repeated measures designs, and either direct or implicit manipulations of circulating androgens. In a preliminary report, Kimura and colleagues (Kimura and Hampson 1994; Kimura and Toussaint 1991) found that a sample of young men showed seasonal differences in performance on spatial tests in accordance with the circannual rhythm in testosterone production which occurs in males (Smals and others 1976). This pattern was not apparent in female controls, or on other types of cognitive tests administered for comparison. Consistent with the studies cited above, the lower testosterone concentrations found in spring were associated with significantly more accurate male performance on spatial tests. This suggests that short-term changes in levels of circulating testosterone may be accompanied by corresponding changes in spatial performance in males.

If testosterone or a metabolite of testosterone is directly or indirectly responsible for these effects, then experimental infusion or depletion of testosterone should elicit detectable effects on spatial measures. Janowsky and others (1994), in a recent double-blind, placebo-controlled study, examined the effects of testosterone supplementation on cognitive performance in a group of healthy elderly men exhibiting senescent decline in testosterone levels. Testosterone treatment in this population was associated with significant improvement in spatial cognition, as indexed by the Block Design subtest of the WAIS-R, consistent with the notion of an optimum level of testosterone for spatial functioning. No changes were evident in other cognitive domains sampled in the study. Consistent with these findings, Van Goozen (Van Goozen 1994; Van Goozen and others 1995) examined patterns of cognitive abilities, before and after 3 months of treatment with cross-sex hormones, in 2 samples of transsexual patients undergoing hormone therapy prior to sex reassignment. Administration of testosterone to female-to-male transsexuals produced an improvement on the spatial test, and a reduction in performance on verbal fluency tasks, while the reverse pattern was seen in male-to-female transsexuals receiving antiandrogens and estrogens. Both studies, therefore, provide tentative support for an activational effect of sex steroids on spatial abilities. Though spatial abilities were not examined in the recent study by Loosen and others (1994), several sexual and affective functions were successfully monitored in a group of normal male volunteers before, during, and after administration of a newly developed GnRH antagonist, which induced an acute and reversible gonadal suppression. Ideally, this paradigm might be extended to the study of spatial behaviors.

CONCLUSIONS

Gonadal steroids, through long- and short-term effects in the central nervous system, have been shown to modulate a number of sexually dimorphic behaviors in mammals, including spatial-navigational behaviors. These effects are exerted in pre or perinatal life, and/or during the adult reproductive period, and are subserved by a variety of genomic and nongenomic mechanisms (McEwen 1991). It would not be surprising if the human brain retains some sensitivity to organizational and activational effects of gonadal hormones, even though most human behaviors are highly modifiable by environmental and especially social-learning influences. Although this review has focussed on spatial abilities in particular, it seems likely that gonadal hormone effects might extend to other behavioral and

affective realms as well, some of which may have clinical significance (Seeman and Lang 1990).

Recent evidence raises the possibility that visual-spatial abilities may represent one cognitive domain whose expression is partly a function of gonadal hormone levels in humans. Further studies, especially those involving administration or reductions in sex hormones, are needed to better test this hypothesis. The selectivity of effects reported here to particular cognitive domains, the consistency with existing behavioral studies in animals, and the convergent evidence from a number of different human paradigms strengthen the probability that an explanation invoking direct or indirect actions of gonadal hormones will turn out to be the correct explanation for the observed associations between gonadal hormones and spatial functions.

I would, therefore, like to suggest that gonadal hormones may play some role in the establishment, maintenance, and modulation of spatial cognition in humans. Findings to date, however, are only preliminary and descriptive, and as yet provide no clear answers to a number of important theoretical questions. In particular, the fundamental neural mechanisms responsible for these effects are not yet known. Although this is not the only, or even the primary, aim of most behavioral studies, the lack of convenient technology for visualizing where in the human brain gonadal hormones may be active in vivo has forced investigators in this area to rely primarily on indirect inferences from behavior, an approach that has obvious limitations. One can only speculate as to the possible mechanisms that might underlie these effects at the cellular level; animal studies suggest many diverse possibilities, including variations in steroid-sensitive neurotransmitter systems underlying spatial processes, long- and short-term variations in neuronal ultrastructure or synaptic connectivity, direct neuromodulatory actions of steroids at the cell membrane (Schumacher 1990), or some combination of these or other effects. Whether estradiol and testosterone or their derivatives independently modulate level of spatial functioning in adults is unclear. Testosterone can undergo local conversion to estradiol or other active metabolites, and may also bring about corollary changes in circulating estrogens through feedback mechanisms (Janowsky and others 1994). The possible synergistic or antagonistic effects of other centrally active steroids (Majewska 1992) also needs to be explored.

Even at a strictly behavioral level, researchers are only beginning to understand and characterize the nature of hormonal effects on spatial cognition. It is unclear whether the various subtypes of spatial ability are equally sensitive to sex hormones, or whether they show different patterns of relationship. The information-processing components of spatial performance that are sensitive to gonadal hormones, and therefore responsible for the relationships observed, have not been identified. Researchers also need to define, more precisely, how these relationships may vary across different phases of the human lifespan.

In closing, I would like to point out that behavioral and pharmacological studies, while they involve different approaches, ask different research questions, and focus on different levels of analysis, are useful complements in helping us to understand hormonal effects in the mammalian nervous system. Behavioral studies can help elucidate the functional role of hormones at the level of individual behavior, and may shed light on the broader evolutionary context for these effects.

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