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12 Sex Differences in Spatial Ability: Evolution, Hormones, and the Brain

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In the study of sex differences in spatial ability, multiple levels of explanation—functional, phylogenetic, developmental, and proximate—have made complementary contributions to a more coherent view of a behavioral sex difference and its evolution, development, and neurobiology. In 1985, Wimer and Wimer commented that hippocampal function "has something to do with an adaptive difference in roles played by males and females of at least some species. Both our understanding of the operations performed by the hippocampus and of the nature of gender might benefit if a concerted attempt were made to understand what that something is" (p. 108).

The following year, Gaulin and Fitzgerald (1986) published the first of several papers that would begin to answer the question of why sex differences in the hippocampus have evolved in many species. Subsequent work by these authors and others would predict and find sex differences in the hippocampi of those species in which the sexes differ in the spatial problems confronted over their evolution.

But while evolutionary theory can predict the *presence* of neural sex differences, it cannot by itself predict what these differences will be or what will cause their development. This is because natural selection "sees" behaviors, not the underlying neural architecture. The proximate and ontogenetic causes of sex differences in spatial ability must be uncovered by careful anatomical, histological, cytological, molecular, and behavioral analysis. For example, Jacobs, Gaulin, Sherry, and Hoffman (1990) could predict sex differences in hippocampal volume across species only because previous work had shown that the hippocampus is related to spatial processing. Evolutionary theory could then inform hypotheses about the cross-species distribution of sex differences in the hippocampus. Likewise, behavioral neuroendocrinological research demonstrating the activational effects of sex hormones on spatial ability

informs adaptive hypotheses about when, and in which species, these effects will be most pronounced. This chapter reviews the evolutionary, psychological, endocrinological, and neuroanatomical bases of sex differences in spatial cognition, in the hope of fostering such reciprocal contributions and a multilevel perspective.

Sex Differences

Homo Sapiens

With their influential book, *The Psychology of Sex Differences*, Maccoby and Jacklin (1974) made cognitive sex differences a topic of legitimate study and pointed to spatial ability as the most dramatic among these differences. They argued that, on average, males perform reliably better than females on a wide array of spatial tests. Subsequent meta-analyses (Linn & Petersen, 1985; Voyer, Voyer, & Bryden, 1995) confirmed this overall finding but also divided spatial skills more finely and estimated the magnitude of the sex difference in each of these areas. Using both psychometric (homogeneity of effect sizes) and cognitive (similarity of mental operations) criteria, this body of work has isolated three distinct types of spatial ability: spatial perception, mental rotation, and spatial visualization.

Spatial perception refers to the ability to recognize spatial relationships, for example, the horizontal, in spite of distracting or contradictory information. These tasks typically have a gravitational or kinesthetic component. Examples are the rod-and-frame test and the water-level task. Mental rotation is the ability to imagine two- or three-dimensional (2D, 3D) objects from a perspective other than the one depicted. The most widely used of these is the Vandenberg and Kuse (1978) mental rotation test. Spatial visualization tasks require the disembedding of a simple shape from a complex background. There is some question about whether spatial visualization can be reliably distinguished from what psychometricians call general fluid ability (the ability to form relationships among symbols), which is regarded as a nonspatial cognitive ability (Linn & Petersen, 1985). Examples of spatial visualization tasks include the embedded-figures test, the block design test, and the spatial relations subtest of the differential aptitude test.

Effect sizes (the difference between male and female means expressed in standard deviations) vary dramatically among these types of spatial ability (table 12.1.) The two most recent meta-analyses agree

Table 12.1
A Comparison of Effect Sizes for Three Types of Spatial Ability from Two Large Meta-analyses

	Weighted Effect Size	
Ability	Linn and Petersen, 1985	Voyer et al., 1995
Mental rotation	0.73*	0.56*
Spatial perception	0.44*	0.44*
Spatial visualization	0.13	0.19

*$P < 0.05$.
Note: Effect size is the difference between male and female performance on the same task, means expressed in standard deviations.

that mental rotation shows the largest sex difference and that the questionably spatial factor, spatial visualization, shows the smallest, often failing to reach statistical significance (Linn & Petersen, 1985; Voyer et al., 1995). Effect sizes within each of these three types of spatial ability are also heterogeneous and depend on task, presentation, and scoring details. For example, 2D mental rotation tasks show smaller effect sizes than 3D versions (Voyer et al., 1995). The Vandenberg and Kuse (1978) mental rotation test is a 3D test, but it can be scored one of two ways. Each of the 20 items has two correct and two incorrect answers. Each of the answers can be scored separately, which would yield a perfect score of 40, or an item can be scored correctly if and only if both choices are correct; this method yields a maximum score of 20. Effect sizes for the 40-point method lie between 0.50 and 0.75, whereas for the 20-point method they are larger, between 0.75 and 1.00 (Voyer et al., 1995). This scoring method with this test yields the largest reliable cognitive sex difference, unless, of course, one regards mating preferences as cognitive traits! Sex differences in mental rotations have been observed in African (Mayes & Jahoda, 1988; Owen & Lynn, 1993), East Indian (Owen & Lynn, 1993), and Asian (Mann, Sasanuma, Sakuma, & Masaki, 1990) populations, as well as in Western cultures.

In table 12.1, effect sizes for subjects of all ages are aggregated into a single group. In general, the larger the adult sex difference (as indicated by effect size) for a given type of spatial ability, the earlier during ontogeny that a reliable sex difference emerges. Thus, significant sex differences in mental rotation performance are regularly found even in prepubertal children. Significant sex differences in spatial perception generally arise during puberty. Although sex differences in spatial

visualization are not significant when all ages are aggregated, they are significant among adults, with an effect size of 0.23 (Voyer et al., 1995).

Although they involve significant motor components, targeting and intercepting are sometimes discussed in the context of sexually dimorphic spatial abilities. Here again there is a significant male advantage, and it is measurable from childhood onward (Wickstrom, 1977). Although targeting and intercepting tasks seem to have obvious spatial components, for example, in trajectory prediction, their performance is not highly correlated with performance on the more conventional pencil-and-paper measures of spatial ability discussed above (Watson & Kimura, 1991). On the other hand, given the very large effect sizes observed on targeting tasks (1.0 to 1.5, Watson & Kimura, 1991) and their obvious ecological validity, these spatiomotor domains deserve further study. In particular, these tasks reveal primary abilities that might have been relatively direct targets of selection over human evolution.

Not all spatial tasks show an unambiguous male advantage. Recently, based on predictions from a particular evolutionary perspective, a female advantage on object-*location* memory has been demonstrated (McBurney, Gaulin, Devineni, & Adams, 1997; Silverman & Eals, 1992; Tottenham, Saucier, Elias, & Gutwin, 2003). Both pencil-and-paper and desktop versions of this task have been implemented; all require the ability to recall the location of items in arrays. These tasks tend to show a female advantage, but the effect size is not large (no meta-analysis is yet available), and the female advantage depends on details of the task and the presentation (see, e.g., Dabbs, Chang, Strong, & Milun, 1998; Montello, Lovelace, Golledge, & Self, 1999). For example, making the task explicit by telling participants that they will subsequently be asked about locations, or using abstract objects that are difficult to name, tends to eliminate or even reverse the female advantage (Choi & L'Hirondelle, 2005; Eals & Silverman, 1994). James and Kimura (1997) showed that when the positions of array objects are reciprocally exchanged there is a female advantage, but no sex difference is observed when objects are moved to new positions.

One possible explanation for these inconsistencies is that object-location memory tasks may require multiple cognitive processes, only some of which show a female advantage. Postma, Izendoorn, and De Hann (1998) attempted to decompose object-location memory, arguing that the task requires a spatial encoding of the occupied locations and a correct mapping of particular objects to particular locations. Unfortunately, they did not find a female advantage on any component of the task, so it is difficult to use their findings to explain the pattern of results seen in other studies of object-location memory.

From an evolutionary perspective, it seems appropriate to ask how and why these kinds of spatial skills evolved—what real-world challenges they were designed to address. Navigation is a plausible answer offered by numerous researchers (e.g., Gaulin & FitzGerald, 1986; Gray & Buffery, 1971; Halpern, 2000). There are surprisingly few real-world studies of navigation, probably because of the difficulty of implementing and scoring such tests, and fewer still have investigated the relationship between real-world wayfinding and performance on pencil-and-paper measures. Malinowski (2001) examined mental rotation ability and performance on a large-scale orienteering task among West Point cadets. Subjects were given the task of finding 10 waypoints distributed over an unfamiliar 6-km course, given only map coordinates and simple clues such as "in the valley." Performance on the orienteering task was positively correlated with mental rotation ability among men but not among women.

Montello et al. (1999) administered a large battery of spatial tests, some of them conventional pencil-and-paper tasks, some of them map-based tasks, and some of them involving real-world navigation. Using discriminant analysis, they discovered that performance on these various tasks could accurately assign 92% of their subjects to sex. An examination of those equations led the authors to support the emerging view that, with regard to real-world navigation, the sexes tend to exhibit different styles (e.g., Dabbs et al., 1998). Males exhibit better survey knowledge—they are better at understanding the relationships among locations that could be deduced from an aerial view or from a map. In the same contexts females exhibit better landmark knowledge—they are better at remembering particular locations, their contents, and their sequence along the route. Such a finding might accord well with the observation (above) that females exhibit superior object-location memory. Together these ideas suggest that, when environments are learned from maps, the sex difference in survey knowledge might be eliminated. This prediction agrees with the findings of Montello et al. (1999), but not with those of Malinowski (2001), whose participants were given maps but still exhibited a sex difference. A difference in scale might be responsible—Malinowski's course was an order of magnitude bigger than that of Montello et al. (1999)—but as yet no theory has explained why scale per se might affect male and female performance differently.

Virtual environments have also been used to study spatial problem solving in humans. Although some somatic cues (e.g., proprioceptive and vestibular input) are artificially absent in these studies, virtual environments provide an interesting bridge to the tools traditionally used to study spatial learning in rodents, that is, mazes. Moffat, Hampson, and Hatzipentalis (1998) administered a series of spatial and verbal tasks, along with computer-generated virtual mazes. Factor analysis was used to extract a spatial and a verbal factor from performance on the various nonmaze tests. When performance was measured either in terms of speed or of accuracy, males performed significantly better than females on the virtual mazes. In contrast to the findings of Montello et al. (1999), Moffat et al. (1998) found that virtual maze performance was correlated with their spatial factor in both sexes. On the other hand, they found that the verbal factor was also correlated with maze performance, but only among females. This finding, like the preferential use of landmarks by females, suggests that the sexes use different navigational strategies.

Astur, Ortiz, and Sutherland (1998) implemented a virtual version of the Morris water maze (MWM) task commonly used to study spatial learning in rodents. In the virtual task the subject uses a joystick to move about a "pool" in an attempt to find a hidden platform. The only available cues to the location of the platform are the landmarks and geometric features of the virtual "room" surrounding the pool. Three versions of the task gave progressively more helpful instruction, but all produced a significant male advantage, with an effect size between 0.50 and 1.00. In contrast, a control task in which the platform was visible produced no sex difference, suggesting that motivation, manual skill related to joystick use, and skill moving through virtual space were not causes of the observed sex difference.

In summary, the human data suggest most domains of spatial cognition show a significant male advantage, of at least moderate effect size, at least in adults. This finding holds across scales and presentations, from small-scale, pencil-and-paper and desktop tasks to walking-scale and real-world tasks, as well as for virtual instantiations of these tasks. Object-location memory may show a female advantage, but the effect size is typically small, and the precise task details that produce this sex difference have yet to be specified. In addition, scale may play a role, with larger scales accentuating the sex difference, but this idea requires further research.

Animal Models

A careful meta-analysis of the literature on sex differences in spatial ability among laboratory rodents (Jonasson, 2005) yields a clear but complex picture. This review concentrates on the two most frequently used paradigms, radial arm and water mazes, which isolate quite different components of spatial ability than the tasks used in the human literature. In particular, animal behaviorists have focused on a distinction between working and reference memory. For static objects, location is permanent and can be learned once and simply referred to; the ability to learn and recall such static information is called reference memory. In contrast, some objects are mobile or exhaustible, and thus their location must be frequently updated; the ability to update and retrieve this information is called working memory.

The contrast between working and reference memory can be illustrated in the radial arm maze (RAM) paradigm. A RAM has a central arena and a fixed number of arms, often eight, radiating from that arena. In one type of RAM experiment, a single reward is placed in each of the eight arms; the performance measure is the number of arms visited before all rewards are collected. If the animal remembers where it has collected rewards (working memory), it can attain a perfect score of 8. In a second type of experiment, some arms, perhaps four, never contain any reward. In these protocols, entering an arm where a reward has already been collected is a working-memory error, whereas entering an arm that has never contained a reward is a reference-memory error. In principle, either type of memory can be tested in either type of maze. For example, the MWM would be a reference-memory test if the location of the hidden platform were never changed, and a working-memory test if it were changed from one block of trials to the next.

This literature indicates that there is an overall male advantage, with an effect size of 0.60 in laboratory rodents. Reference-memory only experiments and MWM experiments yield effect sizes of about 0.50, whereas working-memory experiments and RAM experiments yield effect sizes approaching 0.70. Species differences, however, are large: the overall effect size for a sex difference in rats is 0.76 (and is somewhat variable among strains), but for mice it is only 0.18 and does not reach statistical significance (Jonasson, 2005).

The species difference suggests that selection may have been at work, and thus something about the history of these gene pools reflects

the extent to which males and females differ on spatial performance. Unfortunately, it is probably impossible to reconstruct the founding populations and model the relevant selection pressures that might have operated in breeding colonies. A clear suggestion is that it would be useful to know something about male and female spatial performance in wild rodent populations. Some data are available and are reviewed in a theoretical context below. To foreshadow that discussion, polygynous species generally show spatially related sex differences, but monogamous species do not (Gaulin, 1992; Jacobs & Spencer, 1994).

The species difference is also relevant to questions regarding the neurobiology of sex differences in spatial ability. Most studies in this area have used rats as animal models, but several have also examined mice. In species, such as mice, in which consistent spatial sex differences have not been established, how should brain sexual dimorphisms be interpreted? At first it might appear that these brain dimorphisms must be unrelated to spatial ability. But consider that ancestors of laboratory mice may have differed by sex in spatial ability and underlying neurobiology. Many generations of artificial selection may have reduced spatial sex differences but spared some neural dimorphisms. A safer conclusion is that brain dimorphisms in species without spatial sex differences may be necessary but not sufficient for spatial sex differences. A final caveat is that particular brain sex dimorphisms may be sufficient to produce sex differences in spatial behavior in some species or strains but not in others.

There is intriguing evidence that rats may exhibit a strategic sex difference paralleling the apparent landmark-survey preferences seen in women and men, respectively. Solutions to mazes of any type must be based on some sort of reference. Those references could be relatively goal-specific, such as a landmark hung over the hidden platform in an MWM, or more distal, such as the shape of the room in which the maze sits. Experimental manipulation of these two types of cues suggests that female performance is more degraded when landmark cues are altered or withheld, whereas male performance is more adversely affected when global geometry is altered (by moving the maze in the room) or withheld (by curtaining it off) (Kolb & Cioe, 1996; Williams, Barnett, & Meck, 1990; Williams & Meck, 1991). Unfortunately, there have been no attempts to implement studies of object-location memory with rodents, either wild or domesticated.

Summarizing the rodent literature, it seems clear that sex differences in spatial performance are not restricted to humans. Laboratory rats and polygynous species of wild rodents show a distinct male advantage on various types of maze tasks. In laboratory mice and monogamous species of wild rodents, these differences are reduced or absent. Some sex-specific cue preferences also seem to be shared among humans and rodents. The cross-species distribution of these sex differences should constrain our hypothesizing about their proximate and ultimate causes.

Evolution

Theoretical Underpinnings

Because selection shapes organisms to match the demands of their environments and because, within most species, males and females tend to contact the environment in similar ways, the phenotypes of the two sexes tend to evolve in the same direction (Darwin, 1859). The mating context often provides an exception (Darwin, 1871). Particularly when the sexes have different maximal rates of reproduction, they will face different challenges in the mating arena (Clutton-Brock & Vincent, 1991; Trivers, 1972).

Consider the case where males can reproduce more rapidly than females because females invest more in each reproductive venture (e.g., via obligate gestation and lactation in mammals). In such a case, a male can return to the mating pool quite rapidly following copulation without compromising his fitness prospects. On the other hand, high levels of parental investment may remove females from the mating pool for extended periods of time. This means that the mating pool would typically include many more males than females. Such an imbalance produces disproportionate competition among males for mating opportunities. In contrast, females are not expected to compete for something in abundant supply. The result is that selection favors competitive traits in males more than in females, and thus their phenotypes diverge over evolutionary time precisely with respect to the traits that confer an advantage in mating competition. Of course, such traits are not limited to mere weaponry or sexual display structures. Cognitive and motivational systems are likely to be affected as well.

Not only sexual selection but also natural selection may occasionally produce sex differences. A classic case would be feeding niche differentiation in monogamous birds. Because of biparental care, the feeding success of each partner has an impact on the fitness of its mate. In these cases selection may favor adaptations that allow males and

females to exploit different food resources, so as to reduce competition with their mates.

Both sexual selection and natural selection theories have generated hypotheses about the evolutionary basis for sex differences in spatial ability; Sherry and Hampson (1997) provide a review that integrates hormonal and evolutionary perspectives. Most of these hypotheses assume that the cognitive processes measured as "spatial ability" originally evolved in the service of real-world navigation. A further assumption is that relatively large ranges would have favored improvements in these abilities. The baseline observation that any such adaptive hypothesis must explain is that, in general, males perform better than females on most tests of spatial ability. This difference is not restricted to humans, being observed, for example, in laboratory rats and polygynous wild rodents. And as discussed earlier, a spatial domain in which human females outperform males, object-location memory, has also been discovered. A satisfactory evolutionary explanation would account for all three of these observations.

Sexual Selection and Spatial Ability

Sex differences in spatial ability could be explained by sexual selection if, for some reason, increments in spatial ability had a greater effect on the mating success of one sex than the other. Several such theories exist. Alexander (1979) has proposed that human warfare, which potentially eliminates male competitors and may involve the capture of wives, would have favored male range expansion, and hence put a premium on male spatial abilities. Hawkes (1990, 1991) views the hunting of animal prey as energetically inefficient compared to the gathering of plant foods. She thus explains hunting as a form of sexually selected male display; for some reason, females prefer males who are better hunters. The possibility that such males have better-fed offspring falls under a different, natural selection explanation (see below), and in any case is contradicted by Hawkes's data. She concludes that better hunters do have higher reproductive success, but only by virtue of their elevated sexual access to *other men's* wives (Hawkes, 1991). This hypothesis requires the plausible assumption that hunting requires a larger range than gathering.

The last sexual selection hypothesis appeals not to a uniquely human trait, such as warfare or sexual division of foraging labor, but to the mate-searching strategies that are precipitated by various kinds of

mating systems (Gaulin & Hoffman, 1988). Under strongly monogamous mating systems a mated male and female typically share a single range and move through it together. Under certain types of polygynous mating systems females have relatively small ranges, but males travel through a much larger area in search of receptive females. Since mating systems vary across species, this hypothesis predicts that the male advantage observed in rats and people would not be universal.

Unfortunately for the warfare and hunting hypotheses they fail the test of cross-species comparison, a key tool for evaluating adaptive hypotheses. The problem is immediately obvious: rats have neither warfare nor a sexual division of foraging labor, yet show a strong male advantage on spatial tasks. The mating system model has the potential to survive such a test because laboratory rats and contemporary humans derive from ancestral populations that were fundamentally polygynous (Dewsbury, 1981; Murdock, 1967). This is a weak test because it explains only previously known facts. Stronger tests have been performed, however.

Within some genera of wild rodents there are closely related species that differ in mating system; in the genus *Microtus* (voles) some species are strongly monogamous, while others are polygynous. In these species, evidence suggests that the larger male range in polygynous species is indeed related to competition for mates because the sex difference disappears outside the breeding season (Gaulin, 1992; Gaulin & FitzGerald, 1988). Controlled field and laboratory tests of range size and spatial ability indicate that the male advantage in spatial ability is indeed absent in monogamous species (Gaulin & FitzGerald, 1986, 1989). Parallel tests indicate that the male advantage in polygynous species is not due to sex differences in activity levels, spatial experience, or motivation (Gaulin, FitzGerald, & Wartell, 1990; Gaulin & Wartell, 1990).

The hippocampus, a brain structure known to be important for spatial processing (see below), shows parallel variation: there is no sex difference in the size of this structure in a monogamous vole species, whereas males have significantly larger hippocampi in a polygynous congener (Jacobs et al., 1990). Parallel but weaker evidence comes from wild kangaroo rats, where only polygynous species have been tested (Jacobs & Spencer, 1994). (See also Sherry, Jacobs, and Gaulin (1992) for a review of these and related data on the cross-species distribution of hippocampal size.)

Thus, insofar as the influence of sexual selection is concerned, only the mating system hypothesis can explain why some species exhibit and

some species lack sex differences in spatial ability (Jones, Braithwaite, & Healy, 2003).

Natural Selection and Spatial Ability

Here again, a successful hypothesis must offer a reason why range expansion would enhance fitness more in one sex than the other. Existing hypotheses appeal to either life history or foraging ecology.

Greenwood (1980) has noted that many species exhibit sexually dimorphic dispersal patterns, with one sex remaining in the natal area and the other dispersing a considerable distance before it enters the breeding population. An assumption of this perspective is that the dispersing sex requires superior spatial ability. Theory and cross-species data agree that dispersal patterns are related to resource defense. In species where males defend reproductively relevant resources, females are the dispersing sex. Because in humans male resource defense and female dispersal are the norm, the prediction of this hypothesis—superior female spatial ability—is clearly false, except perhaps in the realm of object-location memory.

There is a natural selection hypothesis that parallels Hawkes's (1990, 1991) hunting model. Under this view (Lovejoy, 1981), male hunting and concomitant range expansion evolved in response to selection for paternal care rather than selection for sexual display. Unfortunately, this theory suffers the same defect as Hawkes's model: it fails the cross-species test, in that male rats neither hunt nor provision their young.

Silverman and Eals (1992) have also attended to sex differences in foraging activity. They argue that hunting animal foods and gathering plant foods each require distinctive kinds of spatial cognition. Their hypothesis would be rejected on the same grounds as Lovejoy's and Hawkes's except that it makes a novel and testable prediction: that there should be distinctive kinds of spatial tasks on which females excel. They argue that because the foraging targets typically exploited by females, plant foods, were immobile, females should have evolved superior memory for the location of objects. They have developed pencil-and-paper and desktop tests of this hypothesis, and have found some support.

Unfortunately, none of these tasks has much ecological validity, in that they do not involve plant foods and have a spatial scale that is very different from the one over which ancestral women would have foraged. Recent field experiments have attempted to remedy these deficiencies and

have confirmed that females more precisely recall the location of food items in a real-world environment (Gaulin, Krasnow, Truxaw, & New, 2005).

Thus, at present, the most plausible evolutionary explanation for the patterns of observed sex differences in human spatial cognition requires the conjunction of two models. Because both chimpanzees and humans are fundamentally polygynous with larger male ranges, we might plausibly assume that our common ancestor was as well. From this viewpoint, sexual selection arising out of male-male competition for access to mates favored an array of superior spatial skills in male protohumans for at least 7 million years. At some later point in human evolution the sexes began to concentrate on different ecological resources. This differential concentration in turn began to favor a distinctive spatial ability in females. This type of cumulative selection (Dawkins, 1986) is a hallmark of the evolutionary process.

Hormones and Development

Selection can create sex differences by favoring responses to sex-specific hormonal regimes. At their most basic level, these responses are molecular. Sex hormones bind to their receptors and modulate gene transcription. Because the sexes differ in the relative amounts of hormones secreted by their gonads, sex differences in gene expression result. Sex hormone–mediated gene transcription affects the growth, development and maintenance of the body, including the nervous system. In this section, we review evidence regarding the hormonal mediation of sex differences in spatial ability, and in the next we look at what neural substrates these hormones may be acting on to create spatial sex differences.

Organizational Hormonal Effects

Animal Models In rats, spatial ability is masculinized by testicular hormones during the perinatal period. Several studies have shown that neonatal castration impairs maze learning in males (Dawson, Cheung, & Lau, 1975; Isgor & Sengelaub, 2003; Joseph, Hess, & Birecree, 1978; Williams et al., 1990) and neonatal testosterone treatment improves maze performance in females (Dawson et al., 1975; Isgor & Sengelaub, 1998, 2003; Joseph et al., 1978; Roof, 1993b; Roof & Havens, 1992; Stewart, Skvarenina, & Pottier, 1975).

At present, however, it is unclear whether the effect of testosterone on spatial performance is mediated by the binding of testosterone to androgen receptors (ARs). This is because many androgens, including testosterone, may be converted into estrogens, such as estradiol, in the brain through a process called *aromatization* (after the enzyme aromatase), which may then masculinize behaviors by binding to estrogen receptors (ERs). Williams and colleagues (Williams et al., 1990; Williams & Meck, 1991) found that neonatal estradiol treatment masculinized spatial ability in female rats, suggesting that spatial sex differences may be ER-mediated. However, a subsequent study (Isgor & Sengelaub, 1998) found that prenatal estradiol treatment did not masculinize MWM performance in female Sprague-Dawley rats, whereas treatment with either testosterone or (the nonaromatizable androgen) dihydrotestosterone did. Of course, it is possible that both ARs and ERs are involved in masculinizing spatial ability in rats. The question of whether spatial ability in rats is masculinized via AR is likely to be answered in the near future by studies of rats with nonfunctional ARs.

Whether androgens masculinize spatial ability in rats directly or via aromatization, there appears to be an optimal level of early androgen exposure beyond which spatial ability actually declines. For example, early androgen treatment improves spatial ability in females but impairs it in gonadally intact males (Roof, 1993b; Roof & Havens, 1992).

Homo Sapiens As in experimental rodents, early androgens appear to masculinize spatial ability in humans, but pubertal androgens may be necessary for complete masculinization. The role of early androgens is supported by multiple lines of evidence. In one study, second-trimester testosterone levels in female fetuses positively predicted spatial abilities when these girls were 7 years old (Grimshaw, Sitarenios, & Finegan, 1995). In another study, girls with male twins exhibited better spatial ability, presumably because of in utero exposure to androgens produced by the male twin (Cole-Harding, Morstad, & Wilson, 1988). Further evidence for the role of early androgens comes from so-called natural experiments, developmental variations characterized by sex-atypical hormone signaling.

Turner syndrome Turner syndrome (TS) represents one such natural experiment. TS individuals have a 45,X karyotype and are phenotypically female, although they tend to be below average in stature and are infertile. Androgen and estrogen production are extremely low due to

undifferentiated gonads (Hojbjerg Gravholt, Svenstrup, Bennett, & Sandahl Christiansen, 1999; Ross et al., 2002), and these hormonal abnormalities may be responsible for specific cognitive deficits in spatial ability (Nijhuis-van der Sanden, Eling, & Otten, 2003). Ross and colleagues (Ross et al., 2003) also found that 2 years of androgen treatment did not improve spatial ability in 26 adolescent (10–14 years) girls with TS. Because pubertal androgens probably improve spatial ability in males (see below), this lack of an effect of pubertal androgens in TS females indicates that early androgens may be necessary for later pubertal organizational effects.

Congenital adrenal hyperplasia Studies of congenital adrenal hyperplasia (CAH) provide further evidence for an organizational effect of androgens. In this condition, an enzyme deficiency causes precursors of cortisol to be shunted down the androgen pathway, leading to an overproduction of androgens from the adrenal glands. Although the hormonal abnormalities of CAH are treated shortly after birth, girls with CAH show signs of elevated prenatal androgen exposure (e.g., virilized genitalia) and tend to be masculinized along several behavioral dimensions (Berenbaum, 1999). Some studies have found CAH girls to exhibit masculinized spatial abilities (Hampson, Rovet, & Altmann, 1998; Hines et al., 2003; Perlman, 1973; Resnick, Berenbaum, Gottesman, & Bouchard, 1986), although others have not (Baker & Ehrhardt, 1974; Helleday, Bartfai, Ritzen, & Forsman, 1994; McGuire, Ryan, & Omenn, 1975). An early CAH study (Perlman, 1973) found that girls with CAH and boys outperformed control girls on one spatial test, but that girls with CAH performed worse than control girls on a spatial test in which no sex difference between controls was found. Because males normally outperform females on this latter test (Weschler Block Design test), this finding raises questions about the representativeness of the control samples. With the exception of this study, however, wherever significant differences between the spatial abilities of CAH and control females have been found, females with CAH have exhibited more masculine spatial abilities. Indeed, a recent meta-analysis (Puts, McDaniel, Jordan, & Breedlove, 2005) concluded that females with CAH have better spatial abilities than do control females across studies.

Complete androgen insensitivity syndrome Studies of females with complete androgen insensitivity syndrome (CAIS) further support the role of androgens in organizing spatial ability. CAIS individuals have a

46,XY karyotype and develop testes that remain undescended in the abdominal cavity. Despite producing normal to high male levels of testosterone, individuals with CAIS have nonfunctional ARs and so are phenotypically female (Imperato-McGinley et al., 1982). CAIS females thus have the potential to provide information about whether androgens masculinize spatial ability and whether they do so via the AR.

Imperato-McGinley and colleagues (Imperato-McGinley, Pichardo, Gautier, Voyer, & Bryden, 1991) found that females with CAIS performed significantly worse on spatial tasks than did their male relatives. On the surface, this finding seems to suggest that androgens masculinize spatial ability via ARs. However, it is also possible that females with CAIS exhibit less masculine spatial abilities because they were socialized in a manner concordant with their phenotypic gender. A more powerful comparison is that between CAIS females and their unaffected (46,XX) female relatives. If spatial ability is AR-mediated, then the spatial abilities of CAIS females should be even less masculine than those of their unaffected female relatives (who produce and receive some androgen message, if less than that of male relatives). In fact, this is precisely what Imperato-McGinley and her colleagues (1991) found. Even this comparison must be interpreted cautiously, however: it is possible that ovarian hormone production in unaffected females caused this difference with CAIS individuals.

Idiopathic hypogonadotropic hypogonadism Thus, CAIS studies indicate that androgens may masculinize spatial ability by acting directly on the AR, and CAH studies suggest that *prenatal* androgens are particularly important. However, evidence from individuals with idiopathic hypogonadotropic hypogonadism (IHH) indicates that pubertal androgenization may be necessary for complete masculinization of spatial ability. IHH males have a 46,XY karyotype but do not produce gonadotropin-releasing hormone (GnRH). GnRH stimulates the anterior pituitary to release luteinizing hormone, causing the testes to produce testosterone. Consequently, untreated IHH men have very low testosterone levels. IHH individuals have normal masculinization in utero, probably due to exposure to maternal luteinizing hormone, and their condition usually is not discovered until they fail to produce the testosterone surge required for puberty.

Hier and Crowley (1982) tested 19 such men on a battery of spatial and verbal tasks. Spatial (but not verbal) performance correlated positively with testicular size, indicating that androgen production affected spatial ability. The men with IHH were also compared with 19 eugonadal men and five men who had developed hypogonadism during or after an otherwise normal puberty. The spatial (but not verbal) scores of the men with IHH were significantly below those of the two control groups, which did not differ significantly from one another. Because both hypogonadal groups had plasma testosterone levels within the normal female range, but only the IHH men had below-normal levels during puberty, these results suggest that pubertal androgens have a positive effect on spatial ability that is undiminished if androgen levels subsequently decline (but see Cappa et al., 1988).

Activational Effects

Androgens appear to organize spatial ability, probably through the AR in humans, and possibly through aromatization in some other mammals. Sometimes gonadal hormones in adulthood also have activational effects on spatial ability, affecting the magnitude of sex differences. We should expect spatial behaviors to remain susceptible to hormonal fluctuations whenever maintaining plasticity in the neural systems underlying spatial ability has some net fitness benefit to the organism. This is likely to pertain when spatial demands change significantly and repeatedly (for example, seasonally). These conditions differ not only across species but also between the sexes.

Animal Models

Testosterone and polygyny In some species, such as meadow voles (*Microtus pennsylvanicus*) and deer mice (*Peromyscus maniculatus*), males expand their home ranges during the breeding season in order to increase access to mates (Galea, Kavaliers, & Ossenkopp, 1996; Galea, Kavaliers, Ossenkopp, & Hampson, 1995; Gaulin & FitzGerald, 1989). In both of these species, males outperform females on laboratory spatial tasks only during the breeding season (Galea et al., 1996; Gaulin & FitzGerald, 1989). These seasonal sex differences are probably due partly to testosterone levels, which are elevated in males during the breeding season (Galea & McEwen, 1999). On the other hand, in relatively nonseasonal species, such as rats, spatial ability appears to be comparatively unresponsive to testosterone after certain critical periods. We have known for decades, for example, that castration of male rats after the

first 10 or so days of life has little effect on spatial ability (Commins, 1932).

Estrogen, fertility, and maternal care Although testosterone probably increases spatial ability and range size in males of seasonally breeding species, estrogens appear to have the opposite effect in intact females. For example, several studies have found impaired maze performance in female rats during days in the estrous cycle when estradiol levels are high (Diaz-Veliz, Soto, Dussaubat, & Mora, 1989; Frye, 1995; Warren & Juraska, 1997). Similarly, range size in the wild and maze performance in the laboratory decrease with elevated estradiol levels during the breeding season in female meadow voles (Galea et al., 1995), and female rats show impaired maze performance during the third trimester of pregnancy, when estradiol levels are highest (Galea et al., 2000). On the other hand, very low levels of estradiol also decrease spatial ability in females: maze performance is impaired by ovariectomy and restored by estradiol administration in female rats (Daniel, Fader, Spencer, & Dohanich, 1997; Luine, Richards, Wu, & Beck, 1998). Sherry and Hampson (1997) have suggested that responsiveness of spatial behavior to estradiol in these species constitutes a pregnancy-related adaptation. According to this hypothesis, the relatively low estradiol levels characteristic of early pregnancy increase spatial ability and ranging to aid females in foraging and locating suitable nest-building sites. Late in pregnancy, high estradiol levels decrease ranging behavior in preparation for nest building and parturition.

Homo Sapiens Although numerous studies purport to demonstrate activational effects of androgens on spatial ability in humans, a careful examination of the literature reveals that such effects are likely to be small or nonexistent. On the other hand, some evidence suggests that estrogens may have inhibitory activational effects on spatial ability in some groups.

Androgens Several studies have found significant relationships between current testosterone levels and spatial ability in between-subjects comparisons. Some of these studies have found simple linear relationships between testosterone levels and spatial ability in men (Silverman, Kastuk, Choi, & Phillips, 1999), pubertal boys (Hassler, 1992) and women (Hausmann, Slabbekoorn, Van Goozen, Cohen-Kettenis, & Gunturkun, 2000). Others have found evidence of a curvilinear relationship (Gouchie & Kimura, 1991; Moffat & Hampson, 1996). In the latter studies, low and high testosterone levels are associated with poorer performance, and intermediate levels are associated with superior performance.

These studies suggest relationships between spatial abilities and testosterone levels, but the shape of the relationships (linear vs. curvilinear) remains unclear. Perhaps more important, between-subjects correlational studies leave questions about the temporal relationships between hormones and spatial ability. The problem with such tests is that circulating levels of hormones in adults may correlate with levels during some earlier life stage. For example, the gonads of some individuals may produce higher than normal androgen levels throughout life. If so, a correlation between adult hormone levels and spatial ability may simply reflect the effects of high androgen production during some earlier organizational period and a tendency for androgen production to continue to be relatively high later in life. Thus, between-subjects correlations often cannot address whether testosterone has activational or organizational effects on spatial ability.

Within-subjects correlational studies can better address whether testosterone activates spatial ability because these studies can show changes in spatial ability that might be caused by fluctuating hormone levels. For example, Moffat and Hampson (1996) found circadian changes in spatial ability that differed significantly by sex. Males tended to improve over the morning, whereas females exhibited the opposite trend. Because testosterone levels decrease over the morning in both sexes, and assuming that high testosterone levels augment female spatial ability but impair it in males, Moffat and Hampson suggested that the sex difference in performance change was the result of activating effects of testosterone. Although plausible, this hypothesis would be better supported by within-subjects correlations between changes in testosterone levels and changes in spatial performance. Without these data, we are left wondering whether the observed changes in spatial ability correlated with testosterone level changes in either sex, or whether another hormone or some other physiological change was responsible. Indeed, the only study to report these highly relevant correlations (Silverman et al., 1999) found no significant relationship between changes in men's testosterone levels and changes in their 3D mental rotation performance over a 12-hour period.

Of course, the best tests of potential causal relationships between current hormone levels and spatial ability involve hormone manipulations. Demonstrating that hormone treatment elicits a particular

phenotypic change and that removal of treatment abolishes this effect constitutes strong evidence for the activating effects of the hormone on the phenotype. Although no studies of which we are aware have examined the effects of removing testosterone treatment, several have measured spatial performance before and after testosterone treatment.

Hier and Crowley (1982) found no difference in spatial ability after androgen therapy in a small sample of six androgen-deficient men. On the other hand, Van Goozen and colleagues (Van Goozen, Cohen-Kettenis, Gooren, Frijda, & Van de Poll, 1994) reported that 22 female-to-male transsexuals performed better at 2D mental rotation after 3 months of testosterone treatment than shortly before treatment was initiated. The authors interpreted this result as a clear demonstration that "the administration of androgens to females causes a shift in the direction of a masculine pattern of cognitive functioning" (p. 1155). However, no untreated controls were included in this study, so the improvement observed could have been due to practice rather than testosterone treatment.

Indeed, in a subsequent study of both female-to-male and male-to-female transsexuals, this time including male and female controls (Van Goozen, Cohen-Kettenis, Gooren, Frijda, & Van de Poll, 1995), subjects' spatial performance improved over time. The authors also reported that the changes in spatial performance differed significantly between these groups, but it appears that this interaction was driven by a slight decline in spatial performance in male-to-female transsexuals (treated with estrogen and antiandrogen) compared to improvement in the other three groups. In order to show that testosterone treatment improved spatial ability, it would have been necessary to show that testosterone-treated female-to-male transsexuals improved significantly more than did untreated females. Another study by these authors, this time without untreated controls, found similar results in hormone-treated individuals: improvement in testosterone-treated female-to-male transsexuals, and no improvement in estrogen- and antiandrogen-treated male-to-female transsexuals (Slabbekoorn, Van Goozen, Megens, Gooren, & Cohen-Kettenis, 1999). From these articles, it is impossible to determine whether testosterone treatment in adults causes an improvement in spatial ability or whether estrogen treatment inhibits it.

Several studies have performed the appropriate controlled comparisons to address whether testosterone treatment improves spatial learning in adults. Van Goozen and colleagues (Van Goozen, Slabbekoorn, Gooren, Sanders, & Cohen-Kettenis, 2002) again examined changes in spatial performance in hormone-treated transsexuals and untreated controls. Although scores improved on mental rotations tasks, there were no differences between groups in improvement on any of the tasks. Alexander and colleagues (Alexander et al., 1998) also found no improvement in visuospatial performance above that due to practice after 6 or more weeks of testosterone treatment in 10 eugonadal and 33 hypogonadal men. Likewise, Ross et al. (2003) observed no improvement in spatial abilities in 26 androgen-treated TS patients relative to placebo-treated TS controls, and Wolf and colleagues (2000) found no effect of a single testosterone injection relative to placebo in 30 elderly men.

O'Connor, Archer, Hair, and Wu (2001), in a well-designed, double-blind, placebo-controlled experiment, also found that testosterone treatment did not affect spatial ability in seven hypogonadal men relative to controls. On the other hand, these researchers observed a significant effect of testosterone treatment in eugonadal men. Whereas placebo group performance increased over three testing sessions, the performance of the testosterone-treated eugonadal group decreased on the second testing session and then showed normal improvement on the third. One interpretation of these results is that, within the normal female-male range, testosterone has little activational effect on spatial performance, but supraphysiological levels of circulating androgens (such as those in androgen-treated eugonadal men) impair spatial performance. However, given that another study (Alexander et al., 1998) failed to find an effect of testosterone treatment on eugonadal men of the same age group, this interpretation should be made cautiously.

Another placebo-controlled double-blind experiment found a significant effect of testosterone treatment on spatial performance in elderly men, but these results are peculiar as well. Janowsky, Oviatt, and Orwoll (1994) observed no significant difference in spatial performance between testosterone-treated and placebo-treated elderly men after 12 weeks of treatment. However, the testosterone-treated men improved slightly between tests, whereas the performance of the placebo-treated men decreased slightly, resulting in a significant interaction between treatment group and testing session. What seems most noteworthy is not the improvement in the testosterone-treated group but the lack of improvement in the placebo-treated group. Several studies (Alexander et al., 1998; O'Connor et al., 2001; Van Goozen et al., 1995, 2002; Wolf et al., 2000) have shown significant improvement with practice in

untreated or placebo-treated controls on a variety of spatial tasks (including the block design task used by Janowsky et al.) over a range of between-test intervals subsuming that used by Janowsky et al. Thus, the significant "effect" of testosterone observed in this study may have been due to the absence of normal task learning in the control group.

In general, these findings—no within-subjects correlations between changes in testosterone levels and changes in spatial ability, and evidence against a testosterone treatment effect—suggest that, at least within the normal range of circulating levels, testosterone has no activational effect on spatial ability in humans. Perhaps this should not be surprising in a species with very low breeding seasonality.

Estrogens On the other hand, menstrual cycle variation in spatial performance (Hampson, 1990a, 1990b; Hampson & Kimura, 1988; Hausmann et al., 2000; Phillips & Silverman, 1997), between-subjects correlations (Hausmann et al., 2000) and the possible treatment effects of estrogens (Slabbekoorn et al., 1999; Van Goozen et al., 1995) suggest that estrogen may have inhibitory activating effects on spatial learning. Other studies have found no effect of estrogen treatment, however. Miles, Green, Sanders, and Hines (1998) and Van Goozen et al. (2002) found no effect of estrogen and antiandrogen treatment on mental rotation performance on male-to-female transsexuals. Moreover, in postmenopausal women, estrogen replacement *improved* performance on a prefrontal cortex/working memory-related spatial task (Duff & Hampson, 2000). Differences between studies in treatment groups (males vs. females, normally cycling vs. postmenopausal women), hormone treatments, and spatial tests may explain these discrepancies. In particular, estrogens may have an inverted U-shaped relationship to spatial ability in women, such that intermediate levels are associated with optimal spatial ability, as in some rodents.

The Brain

Sex-specific hormonal milieus appear to play a major role in causing sex differences in spatial ability, and they may do so by operating on brain regions such as the hippocampus, which is often larger in the sex with superior spatial ability. However, knowing, for example, that male meadow voles have larger hippocampi than females is not particularly informative about what precisely is causing spatial sex differences at the

proximate level. Moreover, selection for superior spatial abilities in one sex may not always lead to sex differences in gross measures like hippocampal size. The neural substrate for spatial sex differences may be subtler, including differences in the sizes of smaller brains regions; differences in cell soma size, neuron density, or dendritic arborization; differences at the molecular level; or widely distributed but subtle differences in any of these measures, to name a few possibilities. The next sections review such finer-scale neural sex differences and their hormonal mediation in mammalian species that exhibit sex differences in spatial behavior.

The Hippocampal Complex

Animal Models The hippocampal complex is located in the medial temporal lobe and is associated with episodic memory and especially with spatial memory and navigation. In humans, the right hippocampus appears particularly important for spatial learning and recall (Maguire, Frackowiak, & Frith, 1996). The hippocampal complex comprises several regions, including the dentate gyrus (DG), the subiculum, and the hippocampus proper (cornu ammonis 1–3, CA1–CA3). Information enters the hippocampus via the DG, where it is transmitted to CA3, to CA1, and then to the subiculum. Males are apparently more reliant than females on the hippocampus for spatial processing in species in which males are advantaged at spatial tasks. This sex difference is illustrated by functional imaging studies in humans and lesion studies in laboratory animals. Lesions to the ventral hippocampus or the entorhinal cortex (the primary cortical input to the hippocampal complex) impair MWM performance in male but not in female Sprague-Dawley rats (Roof, Zhang, Glasier, & Stein, 1993; Silva-Gomez et al., 2003). Thus, the neural substrate for sex differences in spatial ability probably resides partly in the hippocampal complex. Sex differences have been found within several hippocampal subfields, including CA1, CA3, and the DG, as we will see.

Cornu ammonis 1

CA1 sex differences CA1 is one of the final cell fields in the processing and passage of information through the hippocampal complex before output to other brain regions. In species in which males exhibit superior spatial behavior, males tend to have a CA1 that contains larger pyramidal cells (large, multipolar neurons) and, at least in some regions,

is larger in volume. For example, compared to females, male Sprague-Dawley rats have larger pyramidal cell bodies (Isgor & Sengelaub, 1998) and CA1 pyramidal cell field volumes (Isgor & Sengelaub, 1998; Madeira et al., 1992). Madeira and colleagues (1992) also estimated that male rats have more total CA1 pyramidal neurons than females, but Isgor and Sengelaub (1998) did not. Lavenex and colleagues (2000) found no sex difference in CA1 neuronal number among Eastern gray squirrels (in which males have larger home ranges than females), but found larger volumes in two CA1 cell layers (strata oriens and radiatum) in males than in females.

Finally, Cobb and Juraska (2004) found males of one mouse strain to have a larger-volume CA1 than females. But we recall here that across studies, there is no overall sex difference in spatial ability in mice. This suggests that, if a larger CA1 volume is necessary for male spatial superiority, it is not sufficient, or that some mouse strains may indeed display a sex difference on spatial tasks.

Hormonal mediation of CA1 sex differences In Sprague-Dawley rats, early exposure to sex steroids organizes at least two adult CA1 sexual dimorphisms. Isgor and Sengelaub (1998) treated pregnant dams with either flutamide (an antiandrogen), testosterone, estradiol, dihydrotestosterone, or no treatment, and their offspring were examined. Prenatally flutamide-treated males were castrated at birth, and males in another group that received no prenatal treatment were castrated as adults. CA1 pyramidal soma size and pyramidal cell field volume were subsequently measured in adult males and females of various treatment groups. Most notably, prenatal estradiol and testosterone masculinized females on these measures, but prenatal dihydrotestosterone did not. Because testosterone, but not dihydrotestosterone, is aromatizable into estradiol, these results indicate that androgens masculinize CA1 pyramidal soma size and pyramidal cell field volume via aromatization. In addition, adult castration did not feminize males on these measures, suggesting that the activational influences of testicular hormones are not required to masculinize these traits in adult rats.

A puzzling result concerns the prenatally flutamide-treated males. Flutamide blocks androgens by binding to the androgen receptor, so it might seem that flutamide treatment should not affect traits that are masculinized by androgens via aromatization. The finding that flutamide-treated males were not masculinized seemingly implicates AR mediation

and contradicts the female data. Isgor and Sengelaub (1998) suggested that both prenatal testosterone and estradiol may be needed for the masculinization of these traits. However, neonatal castration, rather than flutamide treatment, may explain why males in this group were not masculinized. The critical period for masculinization of these CA1 traits may extend to postnatal day 1, when castration was performed on flutamide-treated males. If so, this group may have exhibited feminine CA1 morphology because castration removed their source of aromatizable testosterone neonatally, a possibility that accords well with the female data.

In contrast, Cobb and Juraska (2004) found no effect of ER-alpha knockout on CA1 volume in a mouse strain that is sexually dimorphic for this trait. One way to reconcile this finding with those of Isgor and Sengelaub (1998) in rats is that CA1 volume masculinization depends on the binding of estrogen to its other receptor (ER-beta). Alternatively, separate hormones may mediate CA1 dimorphisms in different species, or separate hormones may mediate different CA1 dimorphisms in the same species.

Some studies have also found androgen treatment effects on CA1 cell morphology (Leranth, Petnehazy, & MacLusky, 2003) and cytochemistry (Xiao & Jordan, 2002) in adult rats. However, given the lack of an effect of adult androgen manipulations on spatial ability in rats (see above), these neural treatment effects are probably not related to changes in spatial ability.

Cornu ammonis 3

CA3 sex differences CA3 is situated between the DG and CA2. As in CA1, CA3 pyramidal cell bodies and pyramidal cell field volumes are larger in male rats than in females (Isgor & Sengelaub, 1998). Moreover, rats exhibit sex differences in CA3 pyramidal cell dendritic branching (Isgor & Sengelaub, 2003; Juraska, Fitch, & Washburne, 1989) and length (Isgor & Sengelaub, 2003); thus, males' CA3 pyramidal cells have a greater volume of influence than do females' (Isgor & Sengelaub, 2003). Finally, although the number of synapses between mossy fibers (axons projecting from the DG) and the apical dendrites of CA3 pyramidal neurons is the same in male and female Sprague-Dawley rats, the density of such synapses is lower and the volume of the mossy fiber system is greater in males than in females (Madeira, Sousa, & Paula-Barbosa, 1991).

Hormonal mediation of CA3 sex differences Isgor and Sengelaub (2003) demonstrated that neonatal androgens masculinize several sexual dimorphisms in the rat CA3. Sprague-Dawley rats were divided into three low-androgen groups (ovariectomized females, sham-ovariectomized females, neonatally castrated males) and three high-androgen groups (sham-castrated males, neonatally castrated males treated with testosterone propionate from postnatal day 2, females treated with testosterone propionate on postnatal days 3 and 5). Relative to the low-androgen groups, the high-androgen groups were significantly masculinized in CA3 pyramidal cell length, dendritic branching, and volume of influence (volume of the gray matter from which a cell's dendrites can receive input) for nearly all two-group comparisons (Isgor & Sengelaub, 2003). It is not clear from this study whether the aromatization of testosterone into estradiol is involved in the development of any of these CA3 sex dimorphisms.

A previous study by these authors (Isgor & Sengelaub, 1998), however, neatly demonstrates that androgens directly masculinize two other CA3 sexual dimorphisms. In this study, females treated prenatally with testosterone or dihydrotestosterone were masculinized on pyramidal cell field volumes and soma sizes, whereas those treated with estradiol were not. Additionally, males with androgenic influences removed via prenatal flutamide treatment and neonatal castration were feminized on these traits. These results indicate that aromatization of androgen into estrogen is unnecessary for masculinization of CA3 pyramidal cell field volume and soma size. However, this study cannot rule out the possibility that sexual dimorphisms in these traits also depend on early *post*natal androgen action, because it was not demonstrated that similar postnatal treatments would not produce the same results.

Dentate gyrus

DG sex differences The dentate gyrus (so called because of its toothy appearance) consists of three cell layers, including the granule cell layer (DG-GCL). Rodents exhibit several sex differences in the DG-GCL, with males tending to have some combination of the following features: a more lateralized (right greater than left) and perhaps larger DG-GCL, with larger and perhaps more numerous and more densely packed granule cells.

In meadow voles (Galea, Perrot-Sinal, Kavaliers, & Ossenkopp, 1999) and juvenile rats (Roof, 1993a), the DG-GCL is wider in males than in females on the right side only. And in adult rats (Roof & Havens, 1992), the DG-GCL on both sides is wider in males than in females, but the right side is wider than the left side in males only. Interestingly, in both adult (Roof & Havens, 1992) and juvenile (Roof, 1993a) rats, MWM performance correlates with right DG-GCL width. The DG-GCL is also thicker in males than in females in adult (Roof & Havens, 1992) and juvenile (Roof, 1993a) rats. However, at least two studies (Isgor & Sengelaub, 1998; Madeira, Paula-Barbosa, Cadete-Leite, & Tavares, 1988) have found no sex differences in DG-GCL volume in rats. In some mouse strains, DG-GCL volume is also greater on the right than on the left in males only (Tabibnia, Cooke, & Breedlove, 1999).

DG granule cell nuclei tend to be larger in male mice (Wimer & Wimer, 1985) and in adult (Pfaff, 1966) but not juvenile (Roof, 1993a) rats, and male rats have more total DG granule cells than female rats (Madeira et al., 1988; but see Yanai, 1979). Finally, Wimer and Wimer (1985) found that males had higher DG granule cell densities than did females in each of six strains of house mice examined, but Yanai (1979) found no sex differences in this measure in Long-Evans or Wistar rats, suggesting that a sex difference in this measure may be unrelated to sex differences in spatial ability.

Hormonal mediation of DG sex differences Sex differences in the DG appear to be mediated by androgens: early postnatal testosterone treatment masculinizes DG morphology in female rats, and neonatal castration prevents DG masculinization in males. Pfaff (1966) found that neonatal castration prevents masculinization of the nuclear areas of DG neurons. Furthermore, testosterone treatment on postnatal days 3 and 5 masculinizes DG-GCL width in adult (Roof & Havens, 1992) and juvenile (Roof, 1993a) female rats. Early postnatal androgens also masculinize DG-GCL thickness in adult, but not juvenile, female rats (Roof, 1993a). Because juvenile (28-day-old) male and female rats differ in DG-GCL thickness regardless of neonatal testosterone treatment (Roof, 1993a), it is plausible that prenatal hormones contribute to juvenile sex differences in DG-GCL thickness and that early postnatal androgens contribute to maintaining these differences later in life. Roof and Havens (1992) also showed that testosterone treatment of female rats on postnatal days 3 and 5 lateralized DG-GCL width in adults (>90 days of age). This lateralization was also found in male, but not female, controls. A subsequent study (Roof, 1993a) confirmed that the effects of this early

testosterone treatment on DG-GCL laterality were present in female rats by 28 days of age.

By themselves, these results cannot rule out the possibility that androgens contribute to sex differences in DG morphology by first being aromatized into estradiol. However, some evidence indicates that DG-GCL laterality is mediated directly by androgens. Tabibnia et al. (1999) found no laterality in DG-GCL volume in either sex of C57/BL6J mice with a defective structural gene for ARs, despite the fact that both sexes normally exhibit DG-GCL volume laterality in this mouse strain. This indicates that androgens act directly on some aspects of rodent DG morphology without first being aromatized into estradiol. In addition, knockout of ER-alpha in these mice did not affect DG volume, which is probably sexually dimorphic in this strain (Cobb & Juraska, 2004).

Some evidence also indicates that gonadal steroids may exert activational influences in DG morphology in some species. Spatial behavior changes gestationally in female meadow voles (Galea et al., 1995, 2000) and seasonally in males (Gaulin & FitzGerald, 1986), suggesting that the neural substrates for spatial behavior might be responsive to fluctuating sex steroid levels in this species. Indeed, Galea and colleagues (1999) found that DG width correlated with estradiol levels in adult female meadow voles and with testosterone levels in adult males.

Homo Sapiens Few studies have looked for sexual dimorphisms in the human hippocampus. Klekamp, Riedel, Harper, and Kretschmann (1991) reported significantly larger hippocampal volumes in males than in females in postmortem brain sections from adult Australian Aboriginals, but not in those from Caucasians. However, this study did not control for overall brain size, which is larger in males than in females. After controlling for cerebral volume in a quantitative MRI study, Giedd et al. (1996) found that the hippocampus was not significantly ($P = 0.25$) larger in 53 boys ages 4 to 18 than in 46 girls of the same age. However, the right hippocampus grew significantly faster in females (Giedd et al., 1996), and this differential growth may explain the MRI finding of Filipek, Richelme, Kennedy, and Caviness (1994) that young adult females had relatively larger hippocampi than did males.

Neither of these studies found significant sex differences in hippocampal volume laterality. (Giedd et al. found laterality in both sexes, Filipek et al. found laterality in neither.) On the other hand, Zaidel, Esiri, and Oxbury (1994) found greater densities of nucleolated cells on the left compared to the right hippocampi of males but not females in a

sample of 52 unilateral hippocampi surgically removed from epileptic patients. In a voxel-based MRI study of 465 normal adults, men also had significantly more gray matter volume in the hippocampus and entorhinal cortex when white matter, CSF, and age were statistically controlled for (Good et al., 2001).

Finally, hippocampal activation patterns during spatial navigation appear to differ by sex. When navigating a virtual maze, the left hippocampus and the left parahippocampal gyrus were significantly more activated in men than in women relative to a control condition (Gron, Wunderlich, Spitzer, Tomczak, & Riepe, 2000). Indeed, relative to the control condition, these areas were significantly activated only in men. (Recall that the right hippocampus is most activated during spatial cognition in humans.) Using different spatial tests and a different control condition, Blanch, Brennan, Condon, Santosh, and Hadley (2004) found no sex differences in brain activation during spatial navigation. However, male and female performance differed significantly on only one of two spatial tasks used in this study, and the difference was small compared to that reported by Gron and colleagues. Moreover, unlike the control condition used in the Gron et al. study, which consisted of looking at a static screen image and pressing buttons as directed, the control condition used in the Blanch et al. study was itself a spatial task. Thus, it is unclear precisely what was measured in the Blanch et al. study when activation during the control spatial task was subtracted from activation during the experimental spatial task.

The Prefrontal and Parietal Cortices

Animal Models

Prefrontal and parietal cortical sex differences The prefrontal cortex (PFC) is the anterior region of the frontal cortex and is associated with attention to specific events in the environment and with behavioral planning. The PFC receives projections from the parietal cortex, which is associated with spatial perception and spatial working memory. Whereas males seem more reliant on the hippocampus for spatial problem solving, females appear more dependent on the prefrontal and possibly the parietal cortices. Like sex differential reliance on the hippocampus, differential reliance on the prefrontal and parietal cortices is suggested by functional imaging studies in humans and lesion studies in laboratory animals. In one lesion study, Long-Evans rats were PFC-lesioned and

tested on MWM and RAM tasks (Kolb & Cioe, 1996). Females performed worse than nonlesioned controls, but males given identical lesions were unaffected on these tasks. However, males were not entirely unaffected by PFC lesions. On a test in which subjects were required to ignore extramaze cues and attend to a single cue on the maze wall, only lesioned males performed worse than controls (Kolb & Cioe, 1996).

Kolb and Cioe (1996) suggested that these results reflect the different strategies employed by males and females when solving spatial problems. Male rats apparently attend more to "configural" cues (distances and directions) when solving spatial problems and are more impaired in the absence of such cues, whereas females attend more to "specific" cues (landmarks) and are disrupted when landmarks are moved (Williams & Meck, 1991; Williams et al., 1990). This strategic sex difference closely parallels what has been observed in humans. Kolb and Cioe (1996) suggested that PFC lesions may interfere with subjects' ability to shift maze-solving strategies from dominant to less dominant strategies, and that this could explain the sexually dimorphic responses to lesions.

Alternatively, the PFC may aid more directly in tasks requiring landmark use. Because females tend to navigate using landmarks, this would explain why female navigation is more impaired generally by PFC lesions. This could also explain why PFC lesions disrupted landmark task acquisition in males but not in females (Kolb & Cioe, 1996); given females' reliance on landmarks, landmark tasks may be relatively easy for females, and the limited PFC lesions administered by Kolb and Cioe (1996) may have been insufficient to impair females' performance significantly on the single-cue landmark task.

If the PFC is involved in the processing of landmark cues, and if females are more reliant on both landmarks and the PFC for spatial navigation, one might expect some structural sex differences in this region. Indeed, Kolb and Stewart (1991) and Kavaliers, Ossenkopp, Galea, and Kolb (1998) found structural sex differences in both the prefrontal and the parietal cortical regions. Male Sprague-Dawley rats showed more pyramidal cell dendritic branching in parts of a medial PFC region called the anterior cingulate cortex (Kolb & Stewart, 1991). And in meadow voles, females had longer but fewer pyramidal cell dendrites in layer II/III of the prefrontal (cingulate) and parietal cortical regions (Kavaliers et al., 1998). This is a reversal of the pattern observed in the hippocampal complex. That is, given that males have larger cells, more dendritic branching, and so forth, in the hippocampus, on which they are more

reliant for spatial processing, it might be expected that females would be greater on such measures in brain regions, such as the prefrontal and parietal cortices, on which they are more reliant than males. Differential reliance on the prefrontal and parietal cortices and the presence of sex differences in these regions suggest that the brain differences cause the differential reliance. However, it is also possible that these brain dimorphisms reflect sex differences in nonspatial functions, and these possibilities warrant further investigation.

Hormonal mediation of prefrontal and parietal cortical sex differences The developmental causes of sexual dimorphisms in the prefrontal and parietal cortices are poorly understood. However, one study implicates both organization by early androgens and activation by adult ovarian hormones. Stewart and Kolb (1994) found that adult ovariectomy in rats increased the dendritic arbor of layer II/III pyramidal neurons in the parietal cortex and moderately increased apical dendritic spine density, suggesting that ovarian hormones feminize dendritic morphology in the parietal cortex of adult female rats. In addition, intact neonatally testosterone propionate-treated females exhibited greater pyramidal neuronal dendritic arbor than did intact oil-treated females—a result indicating that early androgens masculinize parietal cortical dendritic morphology (Stewart & Kolb, 1994).

Homo Sapiens Little is known about sex differences in the human PFC and how these differences might translate into differential spatial abilities. In an fMRI study, the right superior and inferior parietal lobules and right PFC were significantly more activated during spatial navigation in women than in men (Gron et al., 2000). This finding suggests that there might be some sex differences in the human PFC. In a voxel-based MRI study of 465 normal adults, women had significantly increased gray matter concentration in the parietal cortical mantle compared to men, when white matter, CSF, and age were statistically controlled for (Good et al., 2001).

The Basal Forebrain

Animal Models

Sex differences in the basal forebrain The basal forebrain (BF) is a collection of structures located near the medial and ventral surfaces of the

cerebral hemispheres. The BF has been implicated in attention, motivation, and memory. Cholinergic neurons (those using the neurotransmitter acetylcholine, ACh) in several BF structures, including the medial septal nucleus (MS), the vertical nucleus of the diagonal band of Broca (DBv), and the nucleus basalis magnocellularis (nBM), project to the hippocampus and frontal cortex and are important in memory (Bartus, Dean, Pontecorvo, & Flicker, 1985; Berger-Sweeney, 2003; Davies, 1985; Meck, Church, Wenk, & Olton, 1987). BF cholinergic neurotransmission appears to be involved specifically (but not exclusively) in spatial learning (Bachman, Berger-Sweeney, Coyle, & Hohmann, 1994; Meck, Smith, & Williams, 1988, 1989; Whishaw, 1985). A variety of evidence suggests that sex differences in BF cholinergic neurotransmission may underlie sex differences in spatial performance.

First, cholinergic neurotransmission is sexually dimorphic. Rats differ by sex in the expression of several cholinergic markers over development, including ACh levels (Hortnagl, Berger, Havelec, & Hornykiewicz, 1993), activities of acetylcholinesterase (the enzyme that breaks down ACh at the synapse) (Loy & Sheldon, 1987; Luine, Renner, Heady, & Jones, 1986; Smolen, Smolen, Han, & Collins, 1987) and choline acetyltransferase (the enzyme that synthesizes ACh) (Brown & Brooksbank, 1979; Luine et al., 1986), and uptake of high-affinity choline (a component of ACh) (Miller, 1983).

Second, the spatial performance of male and female rodents is differentially affected by cholinergic manipulations. Embryonic exposure to an inhibitor of acetylcholinesterase impaired female but not male rats on RAM and figure-8 mazes (Levin et al., 2002). On the other hand, dietary perinatal supplementation with choline had a more beneficial effect on RAM performance in male Sprague-Dawley rats compared to females (Williams et al., 1998). Moreover, treatment of adult mice with an ACh antagonist decreased spatial (noncued) MWM performance more in females than in males (Berger-Sweeney, Arnold, Gabeau, & Mills, 1995).

Finally, BF lesions affect spatial learning and associated cortical structure in a sexually dimorphic manner. Only male mice exhibited impaired adult MWM performance as a consequence of neonatal nBM lesions (Arters, Hohmann, Mills, Olaghere, & Berger-Sweeney, 1998). This impairment was greater on spatial than on cued MWM performance, and treatment affected neither activity levels nor learning or retention of nonspatial tasks (Arters et al., 1998). Neonatal nBM lesions also affected cortical layer II/III width differentially by sex, and lesion-related

decreases in cortical layer IV and V widths correlated with spatial MWM performance in males only (Hohmann & Berger-Sweeney, 1998).

For these reasons, it is plausible that sex differences in BF cholinergic neurotransmission contribute to sex differences in spatial ability. However, the relationship between the BF and spatial sex differences is unclear. At least two explanations suggest themselves for the sexually dimorphic effects of neonatal nBM lesions (Arters et al., 1998) discussed earlier. One explanation is that BF afferents affect hippocampal and cortical development, and dimorphisms in these latter regions contribute directly to sex differences in spatial performance. This possibility receives some support from the finding that neonatal nBM lesions had sexually dimorphic effects on cortical structure in adult mice (Hohmann & Berger-Sweeney, 1998).

Another possibility is that the BF is involved in spatial problem solving, and that BF sex differences contribute directly to sex differences in spatial ability. This possibility is supported by the finding that MWM performance is significantly impaired in adult rats treated with an immunotoxin that destroys a type of cholinergic BF neurons (LeBlanc et al., 1999). Furthermore, some lesioned animals received cholinergic neuron grafts to the hippocampus. Grafted animals exhibited greater cholinergic innervation to the DG, and the level of cholinergic innervation to the DG correlated with MWM performance (LeBlanc et al., 1999).

Thus, sexual dimorphisms in the BF may contribute to sex differences in spatial ability by providing sexually dimorphic input to the cortex and hippocampus in adult animals, by playing a role in sexually dimorphic cortical and hippocampal development, or both.

Hormonal mediation of sex differences in the basal forebrain Although no studies of which we are aware have looked for possible organizing effects of sex hormones on cholinergic neurotransmission in the BF specifically, some studies have examined the effects of early sex hormone treatment on cholinergic markers in other brain regions. For example, Libertun, Timiras, and Kragt (1973) found that male and neonatally testosterone-treated female rats exhibited lower choline acetyltransferase activity than did control females in the preoptic-suprachiasmatic area of the hypothalamus, but not in the arcuate-mammillary area or the frontoparietal cortex. Brown and Brooksbank (1979) observed no significant effect of sex or neonatal testosterone treatment on choline acetyltransferase activity in several other rat brain regions. Thus, testosterone may

have organizational effects on BF cholinergic neurotransmission in regions, such as the BF and the preoptic-suprachiasmatic area of the hypothalamus, that exhibit cholinergic sexual dimorphisms.

On the other hand, cholinergic markers in the adult female BF probably depend on the activational effects of estrogens (Gibbs, 1994, 1996, 1997; Gibbs & Aggarwal, 1998; Gibbs, Wu, Hersh, & Pfaff, 1994; Kompoliti et al., 2004; McMillan, Singer, & Dorsa, 1996; Singer, McMillan, Dobie, & Dorsa, 1998) and progesterone (Gibbs, 1996, 2000; Gibbs & Aggarwal, 1998). For example, ovariectomized adult Sprague-Dawley rats that received estrogen replacement exhibited increased cellular levels of choline acetyltransferase mRNA in the MS and nBM (Gibbs et al., 1994). Similar treatment of female rhesus monkeys elevated choline acetyltransferase in the DBv in both young and aged monkeys and decreased numbers of acetylcholinesterase-positive fibers in layer II of the frontal, insular, and cingulate cortices of aged monkeys (Kompoliti et al., 2004).

Environment

Hormonal differences cause sexual dimorphisms in spatial ability and its neural substrates. This is clear from experimental manipulations in animal models and from comparisons between members of the same chromosomal sex who differ in hormonal experience. Environmental differences also contribute to sex differences in spatial ability, and this is probably especially true in humans (e.g., Tracy, 1987). Although a consideration of environmental contributions to sex differences in spatial ability is beyond the scope of this chapter, we have already seen how performance in certain spatial tasks improves with practice.

Finally, it is important to consider the interaction between sex and environment. Sometimes an environmental change may increase or decrease a brain measure equally in both sexes. But often the effects of an environmental manipulation depend on the sex of the animal. Thus, a sex difference in one environment may be smaller, nonexistent, or even reversed in another. For example, the hippocampi of male and female laboratory rodents differ in their responses to stress and stress-related hormones. Adult Wistar rats exposed to restraint stress exhibited sexually dimorphic responses in mineralocorticoid and glucocorticoid (adrenal steroid hormones) receptor expression in several hippocampal areas (Kitraki, Kremmyda, Youlatos, Alexis, & Kittas, 2004). Moreover, treatment of pregnant guinea pigs with glucocorticoid (a stress-related

hormone) resulted in sexually dimorphic responses in mineralocorticoid receptor expression in the hippocampi of their offspring (Liu, Li, & Matthews, 2001; Owen & Matthews, 2003).

These sexually dimorphic molecular responses to stress and stress-related hormones are associated with dimorphic behavioral responses. Restraint stress had divergent effects on spatial ability in Wistar rats, improving MWM performance in females while impairing it in males (Kitraki et al., 2004). Similarly, female Sprague-Dawley rats whose mothers were stressed during gestation exhibited improved RAM performance, while their male counterparts showed poorer performance (Bowman et al., 2004). Finally, females were more impaired than males on water maze performance after early postnatal treatment with a synthetic glucocorticoid (Vicedomini, Nonneman, DeKosky, & Scheff, 1986).

The hippocampal complexes of male and female rats also respond differently to social and sensory stimulation during maturation. Juraska and colleagues (Juraska, Fitch, Henderson, & Rivers, 1985) examined environmental effects on dendritic branching in the DG-GCL of hooded rats. In this study, littermates were randomly divided into environmentally enriched and isolated condition groups. Enriched condition rats were group-housed, given toys, and released daily into an open field with different toy arrangements. Isolated condition rats were individually housed and did not have access to toys or open field exploration. This environmental manipulation affected dendritic branching in the DG-GCL of females but not males. Within the isolated condition group, males showed more dendritic branching per neuron. However, the enriched condition increased dendritic branching in females, reversing the sex difference in dendritic branching in the DG-GCL. In contrast, another study by Juraska and colleagues (1989) found that dendritic branching in CA3 appeared to be more plastic in males in response to this environmental manipulation. Enriched condition males showed less branching in the proximal apical dendrites than did isolated condition males, leading to sex differences in dendritic arborization in CA3 pyramidal cells only in the enriched condition group.

Such sex differences in responsiveness to the environment highlight the degree to which male and female brains may differ across species, but they illustrate another important point: we will not necessarily observe adaptive sex differences in environments (like laboratories) that differ substantially from the environment in which the species evolved (Sherry, Forbes, Khurgel, & Ivy, 1993). Evolutionary theory specifies that

(1) there will be sex differences in spatial ability and related brain regions in species in which males and females have recurrently faced different spatial problems over their evolutionary histories, and (2) these sex differences will develop and persist in environments that are similar to those in which the species evolved. The more an organism's current environment differs from its ancestral one, the less confident we can be that the necessary environmental conditions will exist to allow the organism to develop adaptations to the ancestral environment.

Summary

The largest known cognitive sex differences in humans have been found in the arena of spatial ability. Males outperform females on tasks involving mental rotation and spatial perception, although recent research indicates a spatial domain (spatial-location memory) in which females outperform males. In laboratory rats and polygynous wild rodents, males exhibit superior maze learning, and recent work demonstrates a parallel human sex difference on virtual versions of rodent mazes. The spatial demands of relatively large ranges likely favored superior spatial abilities in males of polygynous mammal species. This sex difference is absent in monogamous rodents and reversed in brood-parasitic birds, in which females experience greater spatial demands. In humans, male superiority on some spatial tasks may have evolved as a result of a combination of polygynous ancestry with broader male ranging patterns and additional spatial demands imposed by hunting. Foraging for immobile resources may have selected for superior object-location memory in human females.

In both humans and rodents, early androgens appear to exert organizational masculinizing effects on spatial ability. It is likely that androgens masculinize rodent spatial ability both via ARs and by aromatization into estradiol before binding to ERs. In humans, spatial ability is probably AR-mediated. Both androgens and estrogens likely have activational effects on spatial ability in some rodents. Responsiveness to fluctuating androgen levels in adult male rodents may be an adaptation to breeding seasonality and accompanying changes in range size. Humans exhibit very low breeding seasonality, and despite assertions to the contrary, current evidence does not support androgens having activational effects on human spatial ability. On the other hand, reasonable data suggest that elevated estrogens in adult female rodents and humans

may diminish spatial ability and behavior. These activational effects may represent an adaptation to changing spatial demands over pregnancy.

Androgens probably masculinize spatial ability by affecting multiple brain regions involved in spatial processing, including the hippocampal complex, the prefrontal and parietal cortices, and the basal forebrain. Masculinization in rodents is AR-mediated for some sexually dimorphic measures in these regions and ER-mediated for others, which accords with the idea that masculinization of rodent spatial ability occurs through steroid binding to both types of receptors.

Within the hippocampal complex, male rats have larger pyramidal cell soma and cell fields in CA1 and CA3 and have greater pyramidal cell dendritic branching and a more voluminous mossy fiber system in CA3 than do females. The DG-GCL is more lateralized and may be larger in some regions in male rats and meadow voles and in males of some mouse strains. DG granule cell nuclei may also be larger in male mice and rats. All of these traits are masculinized by prenatal or early postnatal androgens, but some may remain responsive to estradiol in adult females and to testosterone in adult males of seasonally breeding species. In humans, adult females may have relatively larger hippocampi, but males are apparently more lateralized on some cytological measures and have relatively more gray matter in the hippocampus and its primary cortical input, the entorhinal cortex. Men may also experience greater left hippocampal and parahippocampal activation during spatial processing.

By contrast, the parietal lobules and prefrontal cortex may be more activated during spatial navigation in women than in men, and women possess relatively more gray matter in the parietal cortical mantle than do men. In some strata of the prefrontal and parietal cortices of meadow voles, females have longer but fewer pyramidal cell dendrites. And in one area of the medial PFC, male rats appear to have more extensive pyramidal cell dendritic branching. In one study, dendritic arbor in the parietal cortex of female rats was masculinized by neonatal testosterone and by adult ovariectomy, suggesting that early androgens have masculinizing organizational effects and that estrogens have feminizing activational effects on dendritic morphology in these regions.

Some evidence also implicates sex differences in basal forebrain cholinergic neurotransmission in sex differences in spatial ability. This evidence includes sex differences in cholinergic neurotransmission and in the effects of cholinergic manipulations and neonatal BF lesions on spatial performance. The BF may affect spatial ability by direct

involvement in spatial processing, by affecting the development of the cortex and hippocampus, or both.

In conclusion, the studies reviewed here in aggregate make it clear that there are widespread sex differences in spatial reasoning ability across mammalian species, including humans, such that males on average perform better than females on most tasks. Of course, there are some tasks on which females display better performance, including object-location memory in humans, which suggests that sex differences in spatial ability may be very specific for particular types of spatial reasoning tasks. The task specificity of these sex differences in human performance raises the question of whether selection has honed particular sexes to excel on particular tasks or whether cultural influences on the socialization of developing humans contribute to sex differences in performance. These are not mutually exclusive possibilities, but if cultural factors play an important role, then one could expect to see varying levels of sex differences in spatial ability across varying cultures or to see the magnitude of the sex difference in spatial ability change within the span of a few generations, which is sufficient time for culture to change but not for selection to alter the gene pool. There are some data to support both of these possibilities, so there may well be cultural factors mediating some of the sex differences in human spatial ability.

On the other hand, animal models suggest that selection has also contributed to the sex difference in spatial ability in mammals. For example, the several findings that there is a sex difference in spatial ability in one species but no sex difference in another, closely related species, and that the differing mating systems of the two species allow one to predict which will display a sex difference, is powerful evidence of sexual selection at work. Moreover, surveying sex differences in spatial ability across animals also suggests that selection can exaggerate, minimize, or reverse sex differences, indicating that it is an evolutionarily labile or malleable trait. If so, then there must be genes that augment spatial ability more in one sex than the other, which raises the question of what proximate mechanisms could provide such sex-selective augmentation.

Again, animal models inform the debate, as they indicate that steroid hormones, acting either early in development or in adulthood (or both), augment spatial reasoning in males more than in females. Several studies indicate a similar effect of steroid hormones in humans, which strengthens the notion that selection has contributed to sex differences in spatial reasoning in our own species. Those studies might tempt us to conclude that because hormones influence spatial reasoning, there is no role for experience to influence this behavior and therefore no opportunity for culture to exaggerate or minimize sex differences. Such a conclusion would be absurd, for several reasons. Just because steroids have some influence on human spatial reasoning does not in any way preclude other factors, including experience, from also affecting spatial reasoning. More interestingly, it is always possible that steroid hormones affect spatial reasoning by altering the individual's proclivities, leading the individual to seek out experiences that improve spatial reasoning. If so, then social factors could easily influence how fully an individual might indulge proclivities to sharpen her or his spatial reasoning abilities.

In the future, there will surely be additional comparisons of related species to further detail the evolutionary pressures that promote a sex difference in spatial reasoning. There will also be studies to flesh out the details of the proximate mechanisms underlying such sex differences: which steroid hormones are responsible, where do they act on the brain, what processes do they modulate there, and what are the consequences for brain development and adult behavior? These studies will be conducted in animal models and will serve to inform future inquiries about sex differences in human spatial reasoning.

The study of sex differences in spatial reasoning ability has already been a fruitful area of research for a deeper understanding of how evolutionary pressures can produce proximate mechanisms to alter the brain and thereby favor adaptive behaviors. We can feel fortunate that these same mechanisms also appear to apply, at least in part, to humans, so that we can look forward to a greater understanding of how evolution affects human behavior as this field of study continues to grow.

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