Journal of Neuroscience Research 95:539–562 (2017)

Review

Sex Differences in Hippocampal Function

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Sex differences in the function of the hippocampus have been observed in numerous mammalian species. However, the magnitude, extent, and specificity of these differences are unclear because they can depend on factors including age, methodology, and environment. This Review will discuss seminal studies examining sex differences in hippocampal memory, neuronal morphology, synaptic plasticity, and cell signaling in humans and rodents. We also describe possible organizational and activational effects of sex steroid hormones during early development, puberty, and adulthood that may lead to sex differences observed in the hippocampus. We conclude by discussing the implications of sex differences in hippocampal function for mental health.

Key words: hippocampus; memory; puberty; adolescence; dendritic spines; plasticity; cell signaling

Few scientific topics have garnered as much recent attention in both popular and scientific culture as sex differences. Books from the popular press and media reports about new scientific findings or gender inequalities in the workplace have sparked a national conversation about the extent to which men and women differ and whether these differences matter for education, employment, and opportunity. In the wake of high-profile cases in which men and women exhibited different reactions to drugs prescribed to relieve sleep disturbances, allergy symptoms, and gastrointestinal distress (Rabin, 2013), the National Institutes of Health (NIH) has dramatically altered its guidelines for grant proposals, now requiring investigators to consider "sex as a biological variable" in their applications (Clayton, 2016). This new dictum for scientists is a long-overdue response to the fact that very few biomedical research studies have historically included female subjects, and even fewer have directly compared effects between males and females. As stated by the NIH's Office of Women's Health, the policy is designed to "expand our currently incomplete knowledge base that plays a critical role in informing the development of sex- and gender-appropriate medical care for women and men" (Clayton, 2016). We applaud the effort driving this policy and recognize that a key element necessary for its success is a more widespread dissemination of information to biomedical scientists about sex differences, or lack thereof, in the brain and behavior. As such, special issues such as this one and others (McCarthy, 2016) should greatly aid in providing a scientific foundation for investigators new to sex-differences research.

Sex differences in cognitive function among humans and nonhuman animals have been reported in earnest for well over 2 decades (Williams et al., 1990; Seymoure et al., 1996; Astur et al., 1998, 2004; Kimura, 1999; Levy et al., 2005). Although the nature and magnitude of these differences have been subject to debate (see, e.g., Joel et al., 2015; McCarthy and Konkle, 2005), compared few studies have been conducted on this subject compared to similar topics in neuroendocrinology (e.g., effects of estrogens on cognition in females). This issue is particularly important for mental health, given the existence of sex differences in the prevalence and symptomatology of disorders such as autism, depression, substance abuse, and Alzheimer's disease (Launer et al., 1999; Pigott, 2003; Kessler et al., 2005; Lejuez et al., 2007; Gillies and

SIGNIFICANCE

Although documented sex differences influence the risks, presentation, and response to treatment for certain psychiatric and neurodegenerative disorders, female subjects have historically been excluded from clinical and preclinical studies. Recent policy changes at federal agencies in the United States and Canada aim to rectify this problem by compelling all applicants to consider sex as a biological variable. Because impaired memory function is a hallmark of disorders that disproportionately affect one sex or the other (e.g., Alzheimer's disease, depression, developmental disabilities), this Review discusses the literature reporting sex differences in hippocampal-dependent memory and hippocampal function among humans, rats, and mice.

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Received 30 April 2016; Revised 28 June 2016; Accepted 11 July 2016

Published online 7 November 2016 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/jnr.23864

McArthur, 2010; Whiteford et al., 2013; Keshavarzi et al., 2014; Christensen et al., 2016). Thus, considerably more research at multiple levels of analysis is needed to fully understand the existence and neurobiological origins of sex differences in cognition. This Review focuses on sex differences in hippocampal function because of this brain region's importance in mediating several types of memory (e.g., spatial, working, contextual, recognition) and its association with memory deficits in numerous neurodegenerative and neuropsychiatric diseases (Gillies and McArthur, 2010; Small et al., 2011). This Review highlights selected sex differences in hippocampus-dependent memory and hippocampal function. We first examine the developmental origins of hippocampal sex differences because so little attention has been paid to sex differences in the perinatal and pubertal periods. We then discuss sex differences in hippocampal memory, neuronal morphology, synaptic plasticity, and cellular functioning in young adult humans and rodents. Although sex differences in aged subjects will be briefly touched upon here, we refer readers to other reviews for a more thorough discussion of the topic (Pawluski et al., 2009; Duarte-Guterman et al., 2015).

Although it is tempting to link sex differences in the hippocampus with sex differences in hippocampus-mediated behavior, it is important to remember that such associations are correlations at best. In fact, even the most robust sex differences in brain morphology (e.g., in the sexually dimorphic nucleus of the preoptic area) are not clearly linked with a specific behavioral output (McCarthy, 2016). Moreover, memory is an exceedingly complex process that can be influenced by numerous endogenous and exogenous factors (e.g., age, stress, intellectual stimulation, physical exercise). Thus, ascribing a particular sex difference in a memory task to a specific sex difference in the hippocampus can be challenging. However, the challenge is well worth undertaking because, the more we understand about the neurobiology of cognition in both sexes, the better treatments can be developed to alleviate the cognitive symptoms of mental illness in both men and women.

SEXUAL DIFFERENTIATION OF THE HIPPOCAMPUS

Perinatal Development

Exposure to sex steroids during the prenatal and early postnatal period regulates sexual differentiation of the brain (MacLusky and Naftolin, 1991; McCarthy and Arnold, 2011; McCarthy et al., 2015; de Vries and Forger, 2015; Forger et al., 2016). Females are typically viewed as the "default" sex in mammals, in that a female phenotype will develop in the absence of androgens made by the testes. When the testes are present, testosterone masculinizes the male brain both prior to and soon after birth. These organizational effects of testosterone in males create sex differences in the brain that lead to differential responses to sex steroid hormones during puberty and adulthood. Testosterone itself is not the key hormone responsible for masculinization in rodents; rather, testosterone must be converted by the enzyme aromatase to 17β-estradiol (E_2), which then triggers the cellular events leading to masculinization via estrogen receptors. However, direct actions of testosterone or its nonaromatizable metabolite dihydrotestosterone (DHT) are required for masculinization in nonhuman primates (Wallen, 2005).

In rodents, masculinization of hippocampal function can be permanently altered during the first 10 days after birth. In rats, males typically exhibit faster learning than females in tasks that measure spatial working and reference memory (although both sexes can learn, and the sex difference depends on task parameters; McCarthy and Konkle, 2005). In one classic study using a 12-arm radial arm maze, Williams and colleagues (1990) found that castration of males prior to postnatal day 10 (PD10) produced impaired female-like working and reference memory, whereas treatment of gonadally intact females with estradiol for 5 days prior to PD10 produced enhanced male-like working and reference memory. Other studies have shown that neonatal testosterone treatment masculinizes working and reference memory in females tested in the radial arm maze and the Morris water maze (Roof, 1993b). Prenatal treatment with antiestrogens or testosterone has comparable effects on spatial reference memory in the Morris water maze, such that superior male performance was reversed by prenatal antiestrogen treatment and inferior female performance was reversed by androgen treatment (Isgor and Sengelaub, 1998). Thus, spatial memory abilities appear to be organized by sex steroids within the first 10 days after birth. Interestingly, the effects are accompanied by parallel hormone-induced alterations in hippocampal morphology, in which the granular cell layer of the dentate gyrus (DG) is smaller in adult females and can be masculinized by neonatal treatment with testosterone (Roof, 1993b). Similarly, the volumes of the hippocampal pyramidal cell layers in CA1 and CA3 are greater in males, as are the dendritic fields in CA3 neurons (Isgor and Sengelaub, 1998, 2003). Moreover, both can be feminized in males by prenatal treatment with antiandrogens and masculinized in females by prenatal administration of testosterone or E_2 (Isgor and Sengelaub, 1998, 2003). These data suggest that sex differences in spatial memory may be driven by morphological changes in the hippocampus that are organized by perinatal exposure to E_2.

Absent from our discussion thus far is consideration of how the process of feminization might affect spatial memory in females. Feminization has been historically viewed as a passive process, i.e., the absence of masculinization. However, exciting new epigenetic findings suggest that feminization is a much more active process than previously thought. These data show that feminization of the rat preoptic area (POA) is achieved via the epigenetic process of DNA methylation, which actively suppresses masculinization of the POA and increases copulatory behaviors (Nugent et al., 2015). Moreover, feminization can occur after the critical period, as illustrated by results

showing that pharmacological inhibition or genetic knockout of DNA methyltransferase (DNMT) activity outside of the critical period masculinizes POA anatomy and sexual behavior in females (Nugent et al., 2015). These data provide the first evidence that 1) feminization occurs via active regulation of DNA methylation and 2) reducing DNA methylation after the critical period leads to masculinization by releasing the male genetic profile from epigenetic suppression. Although the feminizing effects of DNA methylation have not been tested in the perinatal hippocampus, our laboratory has shown that dorsal hippocampal infusion of E_2 in adult ovariectomized females increases hippocampal expression of DNMT3B (Zhao et al., 2010), suggesting that E_2 increases DNA methylation in the adult female hippocampus. This methylation is essential for E_2 to enhance object recognition memory in adult females, as coinfusion of a DNMT inhibitor blocks E_2-induced memory facilitation (Zhao et al., 2010). These data support the notion that E_2-induced suppression of DNA methylation promotes hippocampal memory formation in adult females and raise the possibility that E_2 could suppress DNA methylation in the hippocampus of perinatal females. If so, however, this active feminization would appear to impair hippocampal memory, given that spatial and object recognition memory are worse in gonadally intact adult females than in males (Williams et al., 1990; Roof, 1993b; Seymoure et al., 1996; Frick and Gresack, 2003; Gresack and Frick, 2003). Thus, it will be of interest in future work to determine how DNA methylation of the perinatal hippocampus affects hippocampal memory formation in both sexes.

Puberty

Adolescence is the transitional period from childhood to adulthood. Puberty is a defined process that falls within the adolescent period in which the requisite physical and endocrinological changes necessary occur for sexual maturity (Sisk and Zehr, 2005). These changes include cyclic ovarian hormone production in females, which is characterized by surges of E_2 followed by progesterone, and diurnal testosterone production in males that drives spermatogenesis. The average onset of puberty in humans is 11–13 years for females and 13–15 years for males (Jorgensen et al., 1991; Anderson et al., 2003; Al-Sahab et al., 2010). Puberty in rats occurs at about age PD30–39 in females and PD40–45 in males, as identified by vaginal opening and preputial separation (Koss et al., 2015), but these ages vary between species and strain.

In humans, puberty occurs during a tempestuous adolescent period in which multiple psychosocial changes take place, including shifts in social influence from parents to peers, heightened emotional responses, and increased risk-taking and novelty-seeking behaviors (Arnett, 1999; Spear, 2000). These changes are necessary to facilitate psychological autonomy from parents, establish independence, and optimize future reproductive success (Spear, 2000). Although adolescents like to think they know more than their parents, numerous studies indicate that cognitive function in adolescents has yet to reach adult levels. Adolescents exhibit poorer working memory, attention, and slower processing speeds in many tests of cognition (for reviews see Keating, 1990; Graber et al., 1996; Anderson et al., 2001; Gur et al., 2012). This cognitive immaturity may be due to incomplete brain development; human neuroimaging studies have shown that the hippocampus, neocortex, amygdala, nucleus accumbens, and many other brain areas continue to develop throughout adolescence, often in sex-specific ways (Giedd et al., 1996, 2006; Sowell and Jernigan, 1998; Goddings et al., 2014). Hippocampal volumes increase linearly in late childhood/early adolescence in both sexes but then follow different trajectories in males and females during late adolescence such that a continued increase is observed in males but a slight decrease is found in females (Bramen et al., 2011; Goddings et al., 2014). Although it is tempting to speculate that sex differences in cognitive function and brain structure result from exposure to pubertal hormones, it is unclear the extent to which these differences relate directly to hormones or rather to some combination of biological and psychosocial alterations (Herting et al., 2014).

As in human studies, rodent studies also suggest that the cognitive function and emotional responses of adolescent rodents are not on par with those of adults. For example, adolescent rodents are impaired relative to adults in tests of spatial working memory, avoidance learning, and fear learning (Niemi and Thompson, 1980; Schenk, 1985; Wood and Shors, 1998; Spear, 2000; Rubinow et al., 2009; Wiedenmayer, 2009; Koss et al., 2011). Although the specific contribution of puberty to these memory impairments is unclear, some work has investigated this issue. In humans, one study examining cognitive abilities from childhood to adulthood demonstrated that sex differences in spatial orientation skills occur after puberty (Gur et al., 2012), whereas other reports indicate that sex differences in spatial memory are present prior to puberty. One such study tested prepubescent boys and girls in a virtual Morris water maze, a test of hippocampus-dependent spatial learning and memory that shows robust sex differences in adults favoring males (Astur et al., 1998, 2004; Sandstrom et al., 1998; Sneider et al., 2015). Similar to adults, prepubescent boys outperformed girls, indicating that sex differences in spatial memory are present prior to puberty (Newhouse et al., 2007). This finding suggests that sex differences in spatial memory may be due to organizational effects of hormones that occur in early development. In rodents, similar sex differences have been reported among prepubertal, postpubertal, and adult rats tested in the Morris water maze (Willing and Juraska, 2015). However, another study in rats suggested that female-specific allocentric strategies used in the Morris water maze do not appear until after puberty (Kanit et al., 2000). Effects of puberty have also been observed in other hippocampus-dependent tasks, including trace eye-blink conditioning, a form of associative learning. In adult rats, exposure to an acute stressor facilitates trace eye-blink acquisition of males but impairs

acquisition in females, an effect mediated in females by activational effects of E_2 (Wood and Shors, 1998). In a followup study, stress did not affect conditioning in either sex before puberty and enhanced conditioning in both sexes during puberty (Hodes and Shors, 2005). Thus, males and females appear to be similarly affected by stress prior to and during puberty but to exhibit opposite responses to stress after puberty. Perhaps, the appearance of sex differences in learning and memory after puberty results from heightened stress sensitivity in females and may appear only during stressful situations. These data indicate that puberty may render males and females differentially sensitive to environmental factors, such as stress, that modulate hippocampus-dependent learning and memory. However, few studies have investigated pubertal hormone effects on memory, so the extent to which puberty affects other types of hippocampal memory in both sexes is largely unknown and requires further study.

Long-term memory is generally thought to involve structural alterations in the brain. In particular, dendrites continue to develop well past the critical period in early development, making it more likely for them to be altered by pubertal hormones (Juraska et al., 1990; Harris, 1999). In post mortem brain tissue from middle-aged humans (Barrera et al., 2001) and young adult rats (Markham et al., 2005), the dendritic trees of CA1 hippocampal pyramidal neurons are larger in males than in females. Side-by-side comparisons of male and female dendritic growth during adolescence have not been conducted, but one rat study showed an increase in dendritic arborization from PD44 to PD51, followed by pruning between PD51 and PD55 in female CA1 hippocampal dendrites (Chowdhury et al., 2014). These data suggest that sex differences in adulthood may be due to dendritic pruning in females during adolescence. In support, dendritic pruning occurs in the basolateral amygdala and medial prefrontal cortex (Fig. 1) of female, but not male, rats from PD35 to PD90 (Koss et al., 2014), suggesting sex-specific dendritic pruning in other cognitive brain regions. With respect to hippocampal dendritic spine density, sex differences are not observed in the adult CA1 or CA3 (Gould et al., 1990b; Markham et al., 2005; Salas-Ramirez et al., 2010; Bowman et al., 2015). In both sexes, puberty is associated with CA1 spine loss; spine numbers are significantly higher in prepubertal rats compared with adults but not postpubertal adolescents (Chowdhury et al., 2014). However, the effects of gonadectomy prior to puberty on this spine loss differ by sex, such that prepubertal gonadectomy attenuates the loss of spines in males (Meyer et al., 1978) but not females (Yildirim et al., 2008). These findings suggest that the puberty-induced loss of CA1 spines depends on gonadal function in males but not females. However, such a conclusion would be strengthened by additional research directly comparing hippocampal spine loss in males and female within the same study. In contrast to CA1, a sex difference favoring males in dentate gyrus (DG) neuron number is present prior to and after puberty (Roof, 1993a; Severi et al., 2005), suggesting that sex differences in the DG are organized early in development. However, it is unknown whether the sex differences found in other regions of the hippocampus (i.e., the CA fields) are affected by sex steroids at puberty. An example of pubertal hormones influencing neuron number comes from the medial prefrontal cortex of rats, where a sex difference favoring males emerges only after puberty (Koss et al., 2015). Although both sexes lose prefrontal neurons after puberty, females do so to a greater extent (Markham et al., 2007). Gonadectomy attenuates prefrontal neuron loss in females but not in males, thereby eliminating the sex difference in gonadally intact adults (Koss et al., 2015). Thus, in the medial prefrontal cortex, unlike the DG, pubertal ovarian hormones regulate sex differences in neuron number. Sex differences in hippocampal morphology are not determined solely by hormones and can be influenced postnatally by environmental factors. For example, sex differences favoring males in DG dendritic branching and CA3 proximal dendrites observed in adult rats can be reversed by housing rats in a complex environment immediately postweaning (PD25) through adulthood (for review see Juraska, 1991). These effects demonstrate that sex differences organized by perinatal hormones are plastic and can be influenced by environmental factors after the critical period and possibly around puberty.

Traditional views of puberty hold that hormonal effects during this period are activational in nature rather than organizational. In effect, the role of puberty is simply to activate brain regions that have already been organized by sex hormones during early development. However, work by Cheryl Sisk and colleagues in the posterodorsal medial amygdala (MePD), as well as other regions with large sex differences, has elegantly demonstrated that puberty is an extension of the critical period during which gonadal hormones permanently organize the nervous system (Sisk and Foster, 2004; Sisk and Zehr, 2005; Schulz et al., 2009; Sisk, 2016). The MePD is a sexually dimorphic region in the Syrian hamster that is larger in males than in females. Castrating male hamsters prior to puberty results in a smaller MePD volume that persists into adulthood and cannot be reversed by testosterone replacement in adulthood (De Lorme et al., 2012). These organizational effects of pubertal hormones are required for classic measures of sexual behavior such as ejaculation number and latency, both of which are associated with this brain region. Eliminating pubertal hormones via gonadectomy prior to puberty also produces long-lasting increases in neuron and glia number in the female medial prefrontal cortex (Koss et al., 2015) and in dendritic spine density in the male CA1 (Meyer et al., 1978), but it is unclear whether hormone treatment in adulthood can reverse these changes. Thus, whether the hippocampus is fully differentiated during the neonatal period is an open question that will require further study.

Unfortunately, puberty has been generally overlooked in investigations of sex differences. Although no direct evidence indicates that further sexual differentiation occurs in the hippocampus during puberty, it seems premature to dismiss the idea because this issue has received insufficient study. Future research is warranted to explore

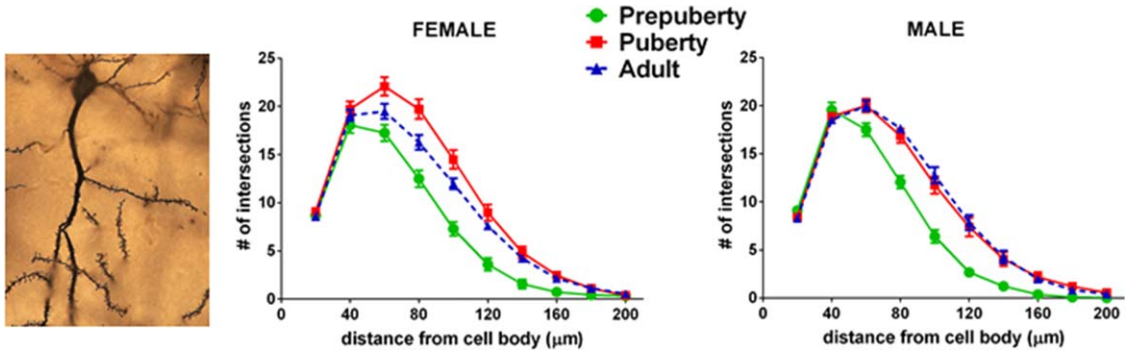

Fig. 1. Dendritic pruning in the medial prefrontal cortex is greater in females during adolescence than in males. The left image is a photograph of a Golgi-impregnated cortical pyramidal cell. Graphs show results of a Sholl sphere analysis, which estimates the amount of dendritic arborization present. Both sexes had significant dendritic growth from P20 to P35, but only females showed a reduction of dendritic material between P35 and P90. Adapted from Koss et al. (2014) with permission.

more fully the organizational and activational actions of pubertal hormones in the hippocampus. As illustrated here, the literature regarding pubertal effects within hippocampus and other cognitive regions of the brain is scant, a situation that we hope will be rectified in the coming years.

SEX DIFFERENCES IN HIPPOCAMPUS-DEPENDENT LEARNING AND MEMORY

The vast majority of studies examining sex differences in hippocampal memory have used young postpubertal adults as subjects. Because subjects are sexually mature, these studies must account for sex steroid hormone fluctuations inherent to female reproductive cycles. Three main approaches have been used to do so. One common approach ignores the cycle and simply compares males and females. A more atypical approach compares males and females in various stages of the cycle. This approach requires vigilant monitoring of the cycle and many more female subjects than males. In rodents, few memory tasks can be conducted within a single day of an estrous stage, which poses challenges for learning and memory tasks that require multiple days of training or testing. In animal models, a final approach involves gonadectomizing subjects and then replacing hormones exogenously. Most studies using this approach have examined effects of hormone treatment on one sex only, typically females. Few reports have directly compared effects of exogenous hormones on both sexes within the same study. Because, many recent reviews have detailed effects of exogenous sex steroid hormones on hippocampal memory in gonadectomized female or male rodents (e.g., Foster, 2012; Luine, 2014; Daniel et al., 2015; Duarte-Guterman et al., 2015; Ervin et al., 2015; Frick et al., 2015; Korol and Pisani, 2015; Tuscher et al., 2015), the following Review focuses largely on sex differences in gonadally intact subjects, although sex differences in the response to exogenous hormones are also discussed. To illustrate the translational relevance of sex differences research in rodents, the discussion focuses on hippocampus-dependent tasks for which analogous data exist for humans and rodents. To this end, the sections below highlight findings from tasks that test spatial memory (Morris water maze, radial arm maze), object recognition, and object location memory.

Spatial Learning and Memory

Sex differences in spatial learning and memory are perhaps the most well studied cognitive sex differences in adult rats because of the ubiquitous use of spatial tasks in behavioral neuroscience. Moreover, the advent of computer virtual environments has allowed spatial learning and memory to be tested in humans using tasks very similar to those used with rodents, thereby increasing the translational value of spatial tasks. Two separate meta-analyses, one focused on human studies and one on rodent studies, concluded that the bulk of research supports sex differences in spatial learning and memory that favor males in young adult humans and rodents (Jonasson, 2005; Hyde, 2016). However, not every study reports sex differences in spatial learning and memory tasks (e.g., Juraska et al., 1984; Bucci et al., 1995; Healy et al., 1999; Frick et al., 2000). In fact, reports of sex differences vary considerably for many reasons, including the type of task and testing protocol, stress associated with the task or environment, and age (Berger-Sweeney et al., 1995; Perrot-Sinal et al., 1996; Roof and Stein, 1999; Frick and Berger-Sweeney, 2001). In rodents, other factors that influence sex differences include species and strain, housing conditions, and even seasonal changes (Galea et al., 1994; Jonasson, 2005). Unfortunately, these variables have made it difficult to replicate sex differences across paradigms and laboratories. With this in mind, the remainder of this section focuses on two widely used tests for studying sex differences in spatial memory in both rodents and humans, the Morris water maze and the radial arm maze. These tasks rely heavily on the hippocampus

(Olton et al., 1978; Morris et al., 1982; Sutherland et al., 1982; Sneider et al., 2011), and both were first developed in rodents and then adapted into virtual computerized versions for human testing to allow better translation between rodents and humans. Although they are not discussed here, it is worth noting that male advantages among humans are reported in other spatial tasks such as route learning (Holding and Holding, 1989; Galea and Kimura, 1993; Postma et al., 2004) and spatial rotation (Parsons et al., 2004; Kaufmann et al., 2008).

The Morris water maze is arguably the most commonly used spatial task in rodent studies and produces larger and more consistent sex differences in spatial memory than the radial arm maze (Jonasson, 2005). In the Morris water maze, rodents must use extramaze cues to locate a hidden escape platform submerged just underneath opaque water in a circular pool. The reliance of navigation in the Morris water maze, and other spatial tasks, on extramaze cues suggests the primary use of allocentric response strategies. However, some evidence suggests a role for egocentric response strategies as well, particularly later in training (Hamilton et al., 2009; Filimon, 2015). In most Morris water maze protocols, the platform remains in the same location throughout testing, so the task is thought to measure spatial reference memory. Although both male and female rodents learn to find the platform, sex differences favoring males have been reported in studies testing young adult rodents in the Morris water maze (e.g., Veng et al., 2003; for review see Jonasson, 2005). However, other studies indicate no difference or a difference favoring females (Lamberty and Gower, 1988; Bucci et al., 1995; Jonasson, 2005; Benoit et al., 2015). Observation of sex differences is confounded by task parameters, including sequence of spatial and cued testing (males outperform females if cued testing comes first; Berger-Sweeney et al., 1995), whether the start position varies for each trial (a consistent start position is associated with no sex difference; Roof and Stein, 1999), stability of landmark cues in the room (males outperform females when major landmark cues move relative to the start position; Roof and Stein, 1999), and inclusion of pretraining (pretraining reduces sex differences; Perrot-Sinal et al., 1996; Jonasson, 2005). Other factors influencing sex differences in rodents include species (male advantages are generally larger in rat studies than in mouse studies) and rearing condition (isolated rearing produces somewhat greater male advantages; Jonasson, 2005). Age and sex steroid hormone levels also influence the observation of sex differences in the water maze; sex differences during spatial and probe trials were observed in middle-aged, but not young adult or aged, rats and mice (Markowska, 1999; Frick et al., 2000). In both species, the sex difference in middle age is associated with the age-related loss of estrous cycling (Markowska, 1999; Frick et al., 2000), suggesting that the loss of estrogen and progesterone cycling with reproductive senescence may contribute to premature spatial memory decline in females. Indeed, young adult female mice tested in the proestrus phase of the estrous cycle (elevated estrogens and progesterone) outperform females tested in the estrus phase (low estrogens and progesterone) and males during spatial probe trials (Frick and Berger-Sweeney, 2001). However, females tested in other phases generally perform similarly to males (Frick and Berger-Sweeney, 2001), suggesting that circulating sex steroid hormones may contribute little to sex differences among young adults. This conclusion is supported by other water maze and radial arm maze studies of rats showing little or no effect of the cycle on task acquisition or effects that depend on water temperature (Frye, 1995; Berry et al., 1997; Stackman et al., 1997; Rubinow et al., 2004). The varied influences of task parameters, species, age, and hormonal milieu make it somewhat difficult to render general conclusions about sex differences in spatial memory among rodents tested in the Morris water maze. However, a meta-analysis of rodent Morris water maze studies published from 1960 to 2003 reported "large reliable" advantages for adult male rats, particularly when no pretraining trials were used and when subjects were raised in isolation (Jonasson, 2005). This analysis suggests a fairly definitive advantage for male rats in the Morris water maze. For mice, smaller female advantages were observed in the Morris water maze (Jonasson, 2005), highlighting a potentially important effect of species on sex differences in this task.

Human versions of the Morris water maze reproduce the maze in a pseudo three-dimensional environment (Fig. 2) in which subjects use keystrokes or joysticks to maneuver through the water from a rodent's-eye perspective. Studies using the virtual Morris water maze in adult humans indicate robust and consistent sex differences favoring males that persists into old age (Sandstrom et al., 1998; Moffat et al., 1998; Astur et al., 1998, 2004; Driscoll et al., 2005; Burkitt et al., 2007; Woolley et al., 2010; Nowak and Moffat, 2011; Nowak et al., 2014). Although it is unclear whether circulating sex steroid hormones contribute to this sex difference, better spatial memory in the virtual water maze and other spatial tasks has been associated with low testosterone levels in males, but higher testosterone levels in females, in some studies (Gouchie and Kimura, 1991; Moffat and Hampson, 1996; Puts et al., 2007; Nowak et al., 2014; but see Driscoll et al., 2005; Burkitt et al., 2007). Sex differences observed from human water maze studies are generally greater and more reliable than those reported from rodent water maze studies. This apparent species difference may result, at least in part, from methodological differences in the tasks. First, humans do not actually move through a three-dimensional environment, and the lack of the sensory, motor, and kinesthetic cues that result from physical navigation may disadvantage women relative to men. Second, because versions of the task for use in humans do not require immersion in a tepid pool of water, differences in the stress associated with swimming may contribute to the discrepancies between humans and rodent studies. However, this latter explanation is unlikely because procedures (like pretraining) that decrease the stress of testing in rodents abolish, rather than amplify, sex differences in the water maze (Lindzey and Winston, 1962; Perrot-Sinal

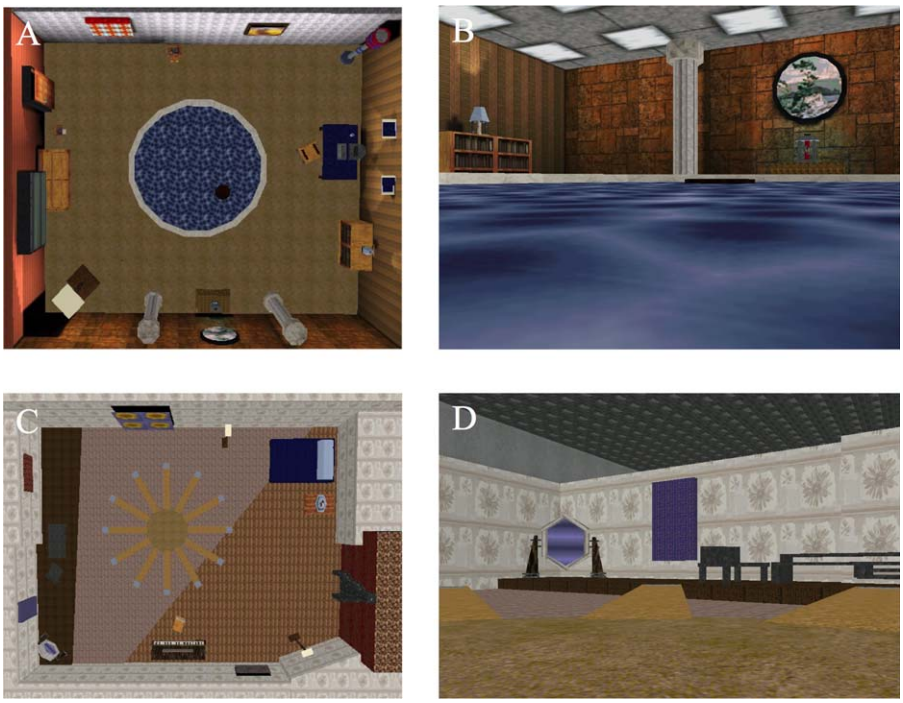

Fig. 2. Overhead and maze-level views of a virtual Morris water maze (**A,B**) and a 12-arm radial arm maze (**C,D**). The escape platform in the water maze is indicated with a black circle. Reprinted from Levy et al. (2005) with permission.

et al., 1996; Beiko et al., 2004). Finally, it is possible that the discrepant magnitude of sex differences in humans and rodents reflects fundamental species differences, although considerably more testing would be needed to support this conclusion.

The radial arm maze differs from the water maze in numerous ways, including shape (eight, 12, or 17 arms radiate evenly from a round center), motivation, number of rewards, amount of pretraining, and type of spatial memory tested. The task was originally designed to test spatial working memory, with working memory errors defined as reentries into an arm that was already visited (Olton and Samuelson, 1976). Later, the maze was adapted to test working and reference memory simultaneously by leaving half of the arms unbaited (Olton and Papas, 1979). A reference memory error is defined as an entry into an arm that is never baited. As described above, many studies show that adult male rats outperform adult female rats in both the working and the reference memory components of the radial arm maze (e.g., Seymoure et al., 1996; Bimonte and Denenberg, 2000; LaBuda et al., 2002; Gresack and Frick, 2003; for reviews see Williams and Meck, 1991; Jonasson, 2005; Luine and Dohanich, 2008). However, some studies show no difference (Juraska et al., 1984) or a difference dependent on locomotor activity (van Haaren et al., 1987). As also discussed above, sex differences in the radial arm maze can be reversed by gonadectomy in males and testosterone or estradiol treatment in females prior to PD10, and so would appear to be organizational in nature. Factors that influence the expression of sex differences in this task include rearing conditions (greater differences in rodents raised in isolation), simultaneous measurement of reference memory and working memory (greater sex differences when both types of memory assessed at the same time), and species (greater effects in rats than in mice; Jonasson, 2005).

Sex differences in the radial arm maze may also be influenced by the different navigation strategies that males and females use in the maze. Males tend to use geometric strategies, thus navigating based on the shape of the environment, whereas females tend to use both geometric and landmark-based allocentric strategies, thus navigating based on the location of certain objects in relation to the shape of the environment (Williams et al., 1990; Galea and Kimura, 1993; Saucier et al., 2002; Astur et al., 2004; Cherney et al., 2008; Andersen et al., 2012; Grissom et al., 2013). Support for this notion comes from work showing that male rats use geometric cues to navigate in the radial arm maze, whereas female rats use both geometric and landmark cues (Williams et al., 1990). Altering the room geometry, but not landmark placement, impairs performance in males, whereas altering geometry or landmarks impairs performance in females (Williams et al., 1990). These sex differences are influenced by organizational effects of sex steroid hormones, as illustrated by findings showing that neonatal castration in males produces female-like use of both geometry and landmarks, whereas neonatal estradiol treatment in females produces

male-like use of geometry only (Williams et al., 1990). Based on these data, it was suggested that greater sex differences would be observed when more landmarks are present because females would be disadvantaged by the additional time necessary to process numerous landmarks in addition to room geometry (Williams et al., 1990; Seymoure et al., 1996). Indeed, spatial mapping based on relationships among multiple cues (i.e., locale strategies) is associated with slower response speeds than orienting using a single cue or body position (i.e., taxon strategies; Whishaw, 1998). However, one study found that rats of both sexes actually made fewer working memory errors in a 17-arm radial arm maze when provided with many cues relative to those provided with few cues (Seymoure et al., 1996). Thus, increasing the number of landmarks present in this experiment did not reduce the sex difference favoring males. Similarly, raising rats in a complex environment improved memory in both sexes and did not eliminate the sex difference favoring males (Seymoure et al., 1996). Together, these data suggest that a robust male advantage for spatial working memory in the radial arm maze that generalizes across numerous experimental conditions.

Spatial strategy use in female rats is influenced by circulating sex steroid hormones, as illustrated by findings showing that females use different strategies in different phases of the estrous cycle. Rats are more likely to use a landmark-based allocentric strategy during proestrus, whereas they use more egocentric or mixed strategies during diestrus and estrus (low hormone levels; Korol et al., 2004). The results of multiple followup studies suggest that the changes in strategy use across the cycle are due to an estrogen-induced reduction in hippocampal GABAergic inhibition (McElroy and Korol, 2005; Zurkovsky et al., 2006). Nevertheless, it should be noted that at least one study reported no effect of the estrous cycle in a version of the radial arm maze in which a delay was inserted between the fourth and the fifth arm choices (Stackman et al., 1997). Sex differences in the radial arm maze may also be influenced by stress hormones in rodents; chronic stress impairs working memory in males but enhances working memory in females (for review see Luine, 2002). Thus, although sex differences in the radial arm maze among rodents may be organized early in development, activational effects of steroid hormones in adulthood play key roles in regulating memory expressed in this task.

Surprisingly, human studies indicate no sex differences in working or reference memory in the radial arm maze (Astur et al., 2004; Levy et al., 2005). One study in which no sex difference was found with an eight-arm maze indicated that working memory and reference memory errors correlated with spatial memory measured by mental rotation but not by the virtual Morris water maze (in which there was a large sex difference favoring males; Astur et al., 2004). In a subsequent study, it was reasoned that a more difficult 12-arm maze might produce sex differences, but none emerged (Levy et al., 2005; Fig. 2). It is curious that robust sex differences in humans are observed in the virtual water maze but not in the virtual radial arm maze. One potential explanation is that movement in the radial arm maze is more restricted than in the water maze, which may aid subjects in finding the goal and, thereby, minimize sex differences (Levy et al., 2005). Alternatively, humans may be more easily able to associate a single landmark with each arm in the radial maze, allowing a landmark-based strategy to work as well as a geometric strategy (Levy et al., 2005). The importance of landmarks for women was recently demonstrated in a study using a version of the task in which four of eight arms were initially blocked (Andersen et al., 2012). No sex differences were observed when eight landmarks were available, but men outperformed women when no landmarks were available (Andersen et al., 2012). The reliance of women on landmarks was confirmed by eye-tracking data showing that women fixated on the objects more than men (Andersen et al., 2012). Interestingly, spatial learners of both sexes spent more time fixating on landmarks than response learners during the first trial but not on subsequent trials (Andersen et al., 2012), suggesting that spatial learners may save time in later trials by spending more time initially forming a cognitive map of the environment. This finding is somewhat consistent with the aforementioned idea that landmark strategy use is slower than geometric strategy use. Regardless, the human radial arm maze data suggest the existence of only minimal sex differences that depend on landmark number but support findings from rats indicating that females rely heavily on landmarks for spatial navigation.

Object Memory

Objects in the environment are often used as landmarks for navigation, and it has been proposed that the female proclivity to use landmarks may lead them to encode more information about the identity and location of objects than males. Thus, tasks that test object recognition and object location memory offer another perspective on sex differences in hippocampal function. In rodents, the involvement of the hippocampus in object recognition has been controversial (Mumby, 2001; Dere et al., 2007); however, substantial pharmacological evidence indicates an important role for the dorsal hippocampus in object recognition (Cohen et al., 2013; Cohen and Stackman, 2015; Tuscher et al., 2015). A role for the dorsal hippocampus in memory for object location is well accepted for both rodents and humans (Kessels et al., 2001; Postma et al., 2008). In humans, object recognition and location memories are often tested using two-dimensional object arrays. Subjects first study an object array and then are presented with modified arrays in which new objects are added (to either new locations or locations previously occupied by old objects), old objects are moved from previously occupied positions, or old objects exchange positions with other objects (Fig. 3A–D). Women consistently notice object substitutions and displacements more than men when new objects are

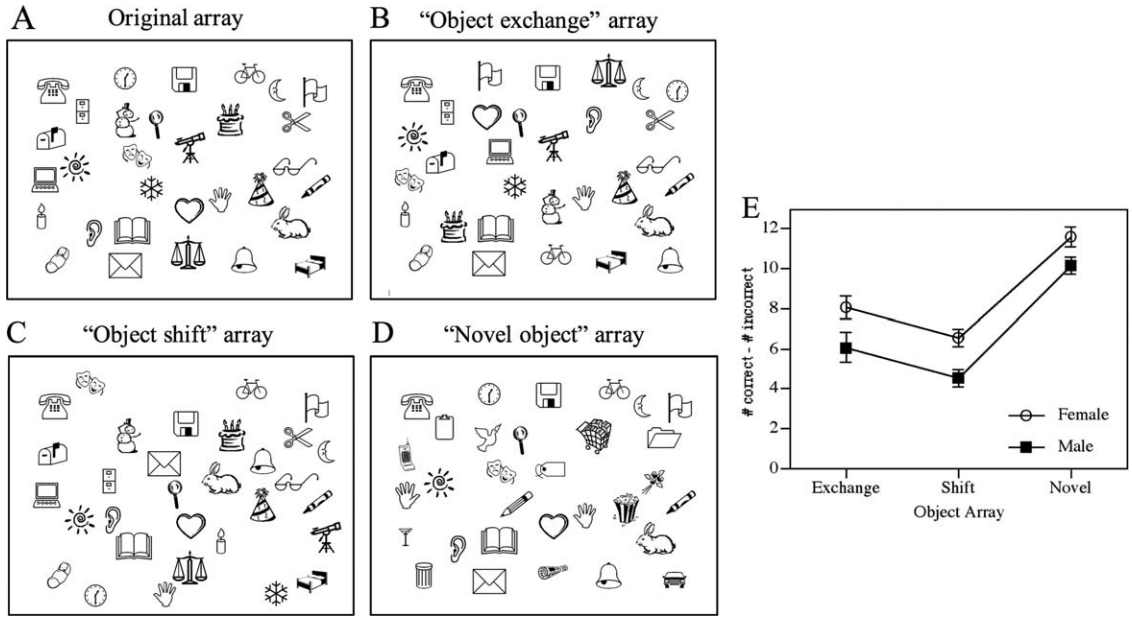

Fig. 3. Women outperform men in remembering the identity and location of objects. Original (**A**), object exchange (**B**), object shift (**C**), and novel object (**D**) arrays used by Levy et al. (2005). As shown in **E**, women were significantly better than men at noticing all object changes ($P < 0.05$ for each condition). Each symbol represents the mean ± SEM. Reprinted from Levy et al. (2005) with permission.

added to an array or old objects are moved to previously occupied positions (Silverman and Eals, 1992; Eals and Silverman, 1994; McBurney et al., 1997; Levy et al., 2005; Fig. 3E), suggesting enhanced object recognition and localization memory relative to men. Some reports suggest that this advantage disappears when old objects are moved to previously unoccupied locations or exchange positions with other old objects (James and Kimura, 1997; Duff and Hampson, 2001). To address this inconsistency, one study examined three array manipulations in which approximately half of the objects changed in the following ways: 1) pairs of old objects exchanged places ("object exchange"), 2) old objects moved to new locations ("object shift"), and 3) new objects were substituted for old objects ("novel object"; Fig. 3A-D; Levy et al., 2005). Women outperformed men in all arrays (Levy et al., 2005), suggesting that women may process object information differently from men. These data could support the notion that women navigate using landmarks more than men, but it should be noted that no sex difference was observed in these same subjects in a 12-arm virtual radial arm maze (Levy et al., 2005). Thus, the extent to which the two-dimensional object arrays inform us about landmark use in spatial navigation is unclear. Another study using the same arrays indicated that heterosexual women and homosexual men performed better in the object exchange, object shift, and novel object arrays (Hassan and Rahman, 2007), suggesting potential hormonal or genetic influences on these sex differences. Although the putative biological bases for these sex differences are unclear, some evidence suggests an activational effect of testosterone in mediating object location memory among women (Postma et al., 2000).

The strong female advantage in object tasks seen in humans is not necessarily apparent in rodents. Rodent tests of object recognition and object location generally involve far fewer objects, although similar manipulations are performed. Most object recognition (OR) and object location (a.k.a., object placement, or OP) tasks use a one-trial sample phase in which rodents are allowed to explore two identical objects in an open arena. After a delay, subjects are returned to the arena where one of the two objects is displaced (OP) or replaced with a new object (OR; Fig. 4A,B). Because rodents are drawn to novelty, they will explore the displaced or novel objects if they remember the identity and location of the familiar object. Sex differences favoring males have been reported in the OP task in both rats and mice (Luine et al., 2002; Luine, 2002; Frick and Gresack, 2003; Bowman, 2005; Salas-Ramirez et al., 2010; but see Benice et al., 2006), which is consistent with male advantages observed in other spatial tasks. However, this male advantage in OP is not observed among aged rats or mice (Benice et al., 2006; Bowman et al., 2006). In rats, this outcome appears to be due to greater age-related deterioration in males compared with females (Bowman et al., 2006). Another study using an object-in-place task (akin to the object exchange condition in humans) showed that male rats outperformed diestrus females at a 30-min, but not a 5-min, delay (Cost et al., 2012). In contrast to the somewhat consistent

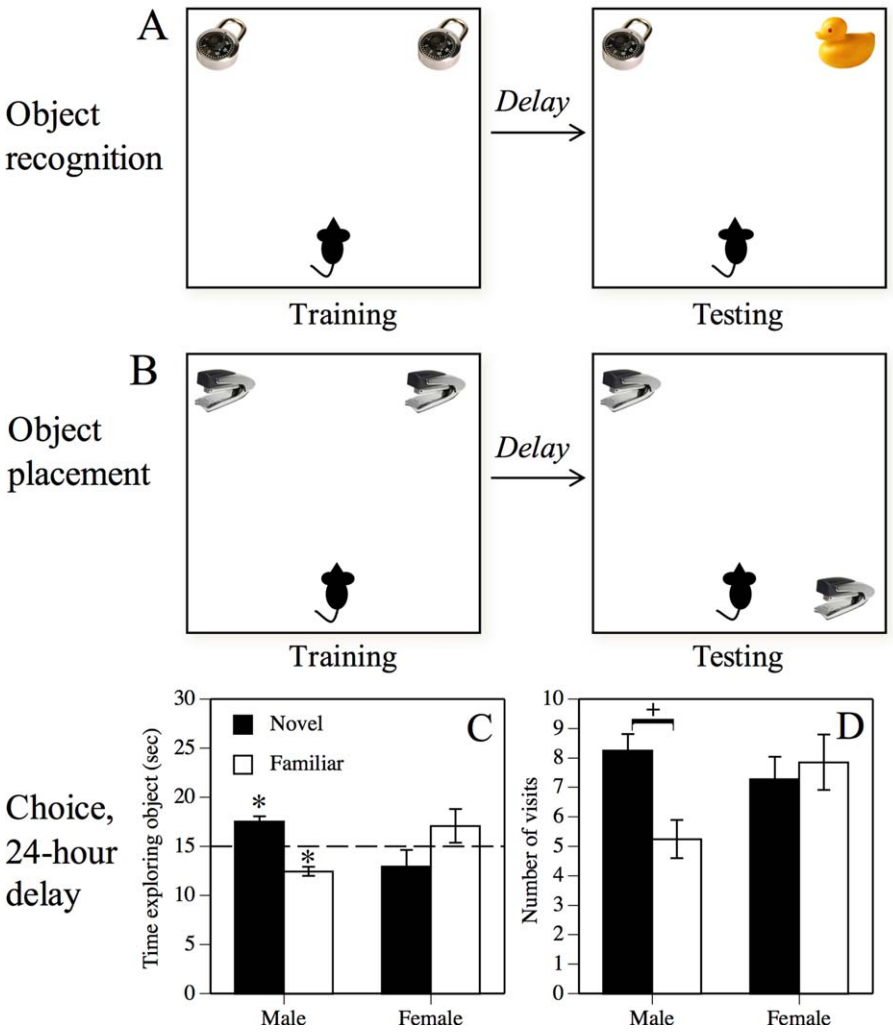

Fig. 4. Schematic diagrams illustrating typical object recognition (**A**) and object placement (**B**) tasks. **C**: In the object recognition task, only male mice spend significantly more time than chance (dashed line at 15 sec, $P < 0.05$) exploring the novel object 24 hr after training. **D**: Males also visit the novel object significantly more than the familiar object ($P < 0.05$), whereas females do not. Each bar represents the mean ± SEM. A and B adapted from Fortress and Frick (2015). C and D adapted from Frick and Gresack (2003) with permission.

male advantage in OP, reports for OR are mixed. Studies of young adult or aged rats and mice report either no sex difference (Benice et al., 2006; Bowman et al., 2006, 2009; Salas-Ramirez et al., 2010) or a sex difference favoring females (Ghi et al., 1999; Saucier et al., 2007; Sutcliffe et al., 2007). Consistent with the latter finding, female rats in proestrus perform better in OR than females in diestrus or metestrus (van Goethem et al., 2012). For mice, data are highly inconsistent. Several studies indicate that males exhibit worse OR (Bettis and Jacobs, 2009, 2012, 2013), whereas others show that females exhibit worse OR (Frick and Gresack, 2003; Fig. 4C,D) or no sex differences (Benice et al., 2006). Although it is difficult to equate the results, given the somewhat different procedural and data analytic methods used, one study that manipulated object similarity showed a female advantage only when the familiar and novel objects were very similar to each other (Bettis and Jacobs, 2012). Using manipulations most similar to those in human object arrays, another mouse study used arrays of five or six objects to test object shift, object exchange, and novel object conditions. Female mice noticed when objects exchanged places and when a novel object was placed in a new or familiar location, whereas males more consistently noticed when a familiar object moved to a novel location (Bettis and Jacobs, 2013). Thus, sex differences in object memory in mice may depend on the specific object change. Overall, however, these data provide some support for the female superiority found in human object array studies. The potential developmental origins

of sex differences in object memory are unclear because no studies have tested sex differences in neonates or adolescents.

Both OR and OP are extremely sensitive to sex steroid hormones in adulthood, suggesting strong activational influences of hormones. The effects of estrogens and progesterone on OR and OP in female rodents have been reviewed recently (Luine, 2015, 2016; Tuscher et al., 2015) and so are discussed here only briefly. The few studies of gonadally intact females indicate that memory in both tasks tends to be best when E_2 and progesterone levels are elevated in the estrous cycle, during pregnancy, and in middle-aged rodents (Tuscher et al., 2015). In ovariectomized female rats and mice, acute E_2 or progesterone administered prior to or within 3 hr after training typically enhances OR and OP memory consolidation in a dose- and delay-dependent manner (Luine, 2016; Tuscher et al., 2015). Far less work has been performed with males, and no study to our knowledge has compared the effects of sex steroid hormones on object memory in males and females within the same study. One study found that gonadectomy impairs OR memory in male rats, and this deficit can be reversed by pretraining systemic long-term treatment with testosterone propionate, but not E_2 (Aubele et al., 2008). A more recent study indicated that posttraining acute E_2 or testosterone enhances OP memory in gonadectomized male rats (Jacome et al., 2016). Similarly, our preliminary data suggest that intrahippocampal infusion of E_2 posttraining enhances OR and OP in gonadally intact male mice (Koss, unpublished). Collectively, the literature on hormonal regulation of OR and OP in adult rodents indicates consistently beneficial effects of E_2, testosterone, and progesterone on object memory in intact or gonadectomized subjects of both sexes.

SEX DIFFERENCES IN HIPPOCAMPAL FORM AND FUNCTION

As discussed for early development, sex differences in numerous aspects of brain morphology and function may underlie sex differences in memory in adults (for recent reviews see Vierk et al., 2014; Frick et al., 2015; Mahmoud et al., 2016; Shors, 2016). The sections below briefly touch on sex differences in hippocampal anatomy and neural function, including hippocampal dendritic morphology, neurogenesis, synaptic plasticity, and cell signaling. The discussion highlights studies that directly compare males and females within the same study, but also includes qualitative comparisons of the effects of exogenous hormones on males and females separately.

Dendritic Morphology

In an early study of adult rats, no sex differences were found in pyramidal cell body area, dendritic branch points, or dendritic spine density in CA1, CA3, or the DG (Gould et al., 1990a). Females exhibited a greater number of primary dendrites in CA3 (Gould et al., 1990a) and a larger branching pattern in dendrites closest to the cell body, but the sex difference was reversed in the more proximal dendrites (Juraska et al., 1989) and was affected by environmentally enriched housing (Juraska et al., 1989). Furthermore, male rats and humans exhibit greater CA1 pyramidal dendritic arborization than females (Barrera et al., 2001; Markham et al., 2005). Together, these findings suggest subtle sex differences that depend highly on the dendritic parameter examined and on environmental factors.

Because synaptic plasticity in adults appears to involve dendritic spines more than dendritic trees (Frankfurt and Luine, 2015), sex differences in spine density may be more likely than other dendritic features to play a role in mnemonic sex differences. However, sex differences in CA1 dendritic spine density have not been observed in numerous rat studies (Gould et al., 1990a; Markham et al., 2005; Salas-Ramirez et al., 2010; Bowman et al., 2015). This apparent lack of effect may mask differences in specific estrous phases. For example, other data suggest that female rats have more CA1 apical spines than males, particularly during proestrus (Shors et al., 2001). Indeed, endogenously high circulating E_2 levels or exogenous E_2 in female rodents increases CA1 spine density (see, e.g., Woolley et al., 1990; Woolley and McEwen, 1992, 1993; Shors et al., 2001). In adult female rats, ovariectomy significantly reduces, and systemic injections of E_2 restore, CA1 dendritic spine density (Woolley and McEwen, 1993; Frick et al., 2004; MacLusky et al., 2005; Wallace et al., 2006; Inagaki et al., 2012). However, extensive handling or behavioral training in the water maze can reduce or eliminate the beneficial effects of E_2 on spines (Frick et al., 2004; Garza-Meilandt et al., 2006). In ovariectomized mice, one study showed that 2 or 5 days of systemic E_2 injections did not increase overall spine density but rather increased thin spines relative to mature mushroom-like spines (Li et al., 2004). However, other studies have shown that a single systemic injection of E_2 or agonists of the estrogen receptors ERα and G-protein-coupled estrogen receptor (GPER) increases CA1 dendritic spine density in ovariectomized mice within 40 min (Phan et al., 2011, 2012; Gabor et al., 2015). Moreover, a single dorsal hippocampal infusion of E_2 increases CA1 apical and basal dendritic spine density in ovariectomized mice 30 min and 2 hr (Fig. 5) later (Tuscher et al., 2016a). Because these studies suggest that estrogenic regulation of dendritic spine density in females occurs quite rapidly, the Li et al. (2004) study that examined spines 2 days after termination of E_2 treatment might have missed this effect. Timing may also play a role in the effects of E_2 on spines in males. Although gonadectomy reduces CA1 spine synapse density in male rats, in vivo studies injecting hormones for 2 days and then measuring spines 2 days later find that systemic androgen, but not E_2, treatment reverses this spine loss (Leranth et al., 2003). In contrast, both in vivo and in vitro studies show that E_2 or an ERα agonist increases CA1 spine density within 2 hr in males (Murakami et al., 2006, 2014; Mukai et al., 2007; Jacome et al., 2016). Thus, spine density increases induced by exogenous E_2

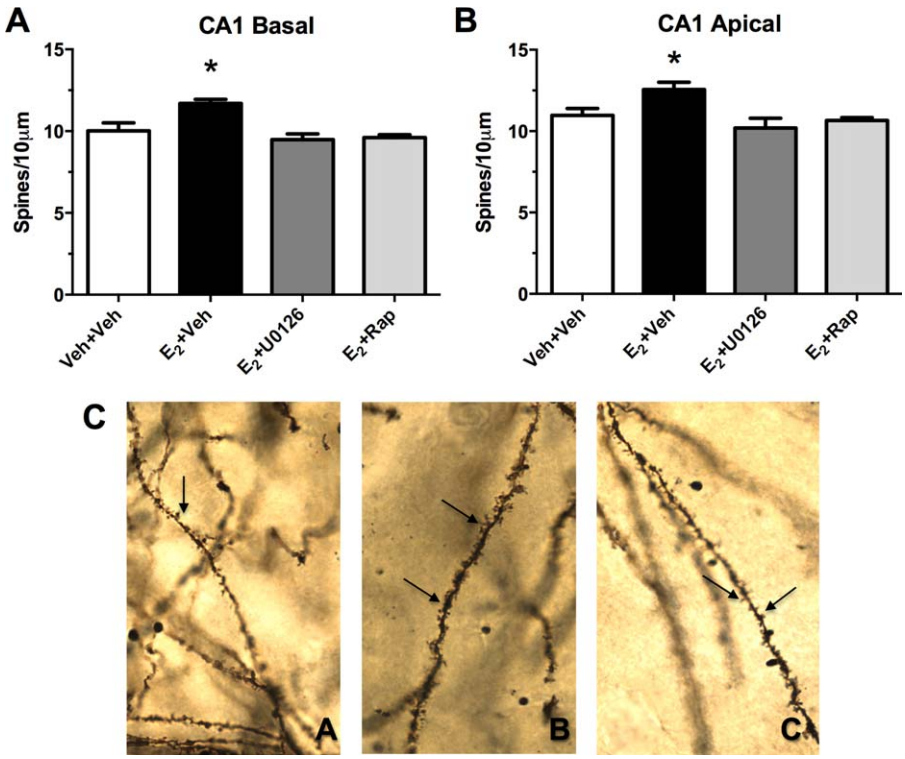

Fig. 5. Intracranial infusion of E_2 significantly increases apical (**A**) and basal (**B**) CA1 dendritic spine density within 2 hr. These effects are blocked by dorsal hippocampal infusion of the ERK activation inhibitor U0126 or the mTOR activation inhibitor rapamycin (Rap). **C**: Photomicrographs of Golgi-impregnated secondary basal dendrites of CA1 pyramidal cells (A, vehicle; B, E_2 + vehicle; C, E_2 + U0126). Arrows denote spines. Under oil, × 63. Adapted from Tuscher et al. (2016a) with permission.

may be rapid and transient in both sexes, unless maintained by further stimulation (see below).

Dendritic spines develop, mature, and retract in direct response to activity-dependent strengthening and weakening of excitatory, glutamatergic neural connections that are needed for memory maintenance over time (De Roo et al., 2008). For embryonic (E18) cortical neuron cultures, a two-step process has been described in which E_2 induces an increase in dendritic spinogenesis that is sustained by subsequent activation of NMDA receptors (Srivastava et al., 2008). This increase is dependent on activation of the ERK signaling pathway and involves the generation of so-called silent synapses that lack AMPA receptors (Srivastava et al., 2008). Consistent with a role for NMDA receptors, activation of NMDA receptors is necessary for E_2-induced spine formation in ovariectomized rats and object recognition memory consolidation in ovariectomized mice (Woolley and McEwen, 1994; Lewis et al., 2008). With respect to cell signaling, numerous pathways have been implicated in estrogenic regulation of dendritic spine density in vitro. In both male and female hippocampal slices, E_2 increases filamentous actin levels and actin polymerization in dendritic spines via the RhoA–RhoA kinase–LIM kinase (LIMK)–cofilin pathway, and blocking this pathway eliminates E_2's effects on spines and long-term potentiation (LTP; Kramár et al., 2009). In male hippocampal slices, increased spine density induced by E_2 or androgens is also blocked by inhibitors that prevent activation of the ERK, protein kinase A (PKA), protein kinase C (PKC), LIMK, or calcium-calmodulin kinase II (CaMKII) signaling pathways (Mukai et al., 2007; Ooishi et al., 2012; Hatanaka et al., 2014; Hasegawa et al., 2015). In the first in vivo study to demonstrate that E_2 increases CA1 dendritic spine density by regulating cell signaling, our group recently showed that activation of ERK or the downstream protein synthesis pathway mammalian target of rapamycin (mTOR) in the dorsal hippocampus is necessary for E_2 to increase spine density in the CA1 of ovariectomized mice 2 hr later (Tuscher et al., 2016a; Fig. 5). Because activation of both signaling pathways in the dorsal hippocampus is also necessary for E_2 to enhance OR memory consolidation in ovariectomized mice (Fortress et al., 2013), these results suggest that regulation of hippocampal dendritic spine density by E_2 may underlie its ability to modulate memory formation. Whether cell signaling is also necessary for E_2 to increase spine density and enhance memory consolidation in males remains unknown.

Neurogenesis

New neurons are produced in the DG during adulthood, and these new neurons are thought to play a key role in facilitating both memory formation and the circuit-level synaptic modifications necessary to alter or forget old memories (Epp et al., 2013; Frankland et al., 2013). Given the importance of neurogenesis for hippocampal memory formation, sex differences in neurogenesis may significantly affect memory in males and females. Female rats in proestrus exhibit more cell proliferation, but not greater cell survival, than males or than females in diestrus or estrus (Tanapat et al., 1999). Although similar sex differences in cell proliferation favoring females have been reported in C57BL/6 mice, other studies have reported no sex differences in several strains, including C57BL/6 (Duarte-Guterman et al., 2015). Thus, it is unclear whether neurogenesis in mice differs between males and females. In rats, ovariectomy reduces DG cell proliferation, and either acute or chronic E_2 increases cell survival (Tanapat et al., 19999, 2005; McClure et al., 2013). However, acute and chronic E_2 have disparate effects on cell proliferation in ovariectomized rats, such that acute treatment with various estrogens and ER agonists increases cell proliferation (Ormerod et al., 2003; Mazzucco et al., 2006; Nagy et al., 2006; Barker and Galea, 2008; Barha et al., 2009), whereas chronic E_2 treatment does not (Perez-Martin et al., 2003; Tanapat et al., 2005; Barker and Galea, 2008; Chan et al., 2014). In males, castration reduces cell survival without affecting cell proliferation (Spritzer and Galea, 2007). Unlike in females, E_2 does not generally increase cell proliferation or cell survival in male rats; however, acute or chronic treatment with testosterone, DHT, or progesterone increases cell survival in gonadectomized males (Spritzer and Galea, 2007; Zhang et al., 2010; Hamson et al., 2013). Collectively, these data suggest sex differences favoring females in neurogenesis among gonadally intact rats and demonstrate the existence of sex differences in the neurogenic response to exogenous sex steroid hormones.

Synaptic Plasticity

Morphological alterations such as those described above are integral for the strengthening and weakening of synaptic connections both within and between structures. High-frequency stimulation of the hippocampal CA fields produces an NMDA-dependent LTP that strengthens synaptic connections. Conversely, low-frequency stimulation decreases excitatory postsynaptic potentials (EPSPs) and produces long-term depression (LTD), which weakens synapses. Both LTP and LTD are affected by endogenous and exogenous sex steroid hormones, although the bulk of research has examined LTP. LTP in CA1 is more difficult to elicit in females than in males (Yang et al., 2004). Male rats also exhibit greater perforant path–granule cell LTP than females (Maren et al., 1994; Maren, 1995). However, LTP in CA1 is enhanced during proestrus relative to males and females in diestrus and estrus (Warren et al., 1995; Good et al., 1999), suggesting that the estrous cycle influences sex differences in LTP. In both male and female rodents, exogenous E_2 increases baseline EPSP amplitude, lowers LTP threshold, and increases LTP amplitude (Teyler et al., 1980; Cordoba-Montoya and Carrer, 1997; Gu et al., 1999; Foy et al., 1999, 2008; Bi et al., 2000; Fugger et al., 2001; Sharrow et al., 2002; Smith and McMahon, 2005, 2006; Smith et al., 2009; Kramár et al., 2009, 2015; Smejkalova and Woolley, 2010; for a recent review see Frick et al., 2015). This potentiation involves alterations in glutamate neurotransmission both pre- and postsynaptically (Smejkalova and Woolley, 2010; Oberlander and Woolley, 2016). Although E_2 facilitates LTP in both sexes, the glutamate receptors involved in the postsynaptic response differ. The effects of E_2 in female rats are mediated by NR2B-containing NMDA receptors, but by AMPA receptors in males (Romeo et al., 2005; Smith and McMahon, 2005, 2006; Kramár et al., 2009). Moreover, the ERs involved in potentiating glutamatergic synapses differ as well. In female rats, ERβ acts presynaptically to increase the probability of glutamate release and the putative membrane ER GPER acts postsynaptically to increase glutamate sensitivity (Oberlander and Woolley, 2016). However, in male rats, presynaptic glutamate release probability is mediated by ERα, and postsynaptic glutamate sensitivity is regulated by ERβ (Oberlander and Woolley, 2016). Collectively these data suggest that, although E_2 increases synaptic potentiation in both sexes, the mechanisms through which it does so differ in males and females. Therefore, much more work will be required to understand better the cellular and molecular mechanisms through which sex steroid hormones such as E_2 influence hippocampal function.

Cell Signaling

The activation of cell signaling pathways allows for the rapid transmission of signals from the plasma membrane to intracellular compartments such as the nucleus and dendrites to promote gene transcription and local protein synthesis, respectively. Numerous cell signaling pathways are necessary for hippocampal memory formation, including PKA, PI3K, CaMKII, and ERK. Thus, one might expect sex differences in memory or hippocampal function to be reflected in sex differences in the activation (phosphorylation) of signaling pathways and/or their downstream transcription factors. Effects of sex steroid hormones on cell signaling may be mediated by intracellular receptors in extranuclear cellular compartments or by membrane receptors. The classical ERs, ERα and ERβ, are considered intracellular ERs, whereas GPER is considered a membrane ER. PR-A and PR-B are intracellular progesterone receptors, and several membrane progesterone receptors have been identified, including mPR and PGRMCs. All three ERs are expressed in dendrites, dendritic spines, axons, and axon terminals in the male and female mouse hippocampus, although expression in females varies across the estrous cycle (Mitterling et al., 2010; Waters et al., 2015). Levels

of extranuclear ERα and ERβ in CA1 and CA3 peak during diestrus; males exhibit lower ERα expression than females in proestrus, diestrus, or estrus, but have ERβ expression similar to that of females in proestrus (Mitterling et al., 2010). Expression of GPER is similar in male and female mice throughout dendrites, spines, and axons in CA1, CA3, and DG (Waters et al., 2015). Intracellular PR expression in CA1 and CA3 peaks during proestrus; expression in males is similar to that of estrus females and higher than that of diestrus females (Mitterling et al., 2010). Thus, although ER and PR expression varies somewhat by sex and estrous stage, these receptors are expressed in both sexes throughout hippocampal neurons, including dendrites, dendritic spines, and axon terminals (Mitterling et al., 2010; Waters et al., 2015), where they are poised to influence cell signaling processes.

Several studies have examined effects of E_2 treatment or learning on phosphorylation of ERK and the downstream transcription factor cAMP response element-binding protein (CREB), which mediates gene transcription via the cAMP response element (CRE) on DNA. In cultured CA3–CA1 hippocampal neurons from 1–2-day-old female rats, bath application of E_2 for 5 minutes increases nuclear CREB phosphorylation and CRE-dependent gene transcription in a manner dependent on activation of ERK (Boulware et al., 2005). Similar effects are not observed in males, suggesting that E_2 does not regulate ERK-dependent CREB phosphorylation or CRE-dependent gene transcription in neonatal males (Boulware et al., 2005). In adult gonadectomized mice, however, a single E_2 injection increases dorsal CA1 CREB phosphorylation within 1 hr in both males and females (Abraham and Herbison, 2005), indicating that sex-dependent effects of E_2 on cell signaling may differ developmentally. Indeed, the ability of bath-applied E_2 rapidly to increase CA1 dendritic spine density and enhance LTP in hippocampal slices from gonadally intact adult male rats is dependent on activation of ERK, PKA, PKC, PI3K, and CaMKII (Hasegawa et al., 2015). Similarly, the ability of testosterone and DHT to increase CA1 spine density in hippocampal slices from gonadally intact adult male rats depends on ERK, PKA, PKC, and LIMK (Hatanaka et al., 2014). Thus, in hippocampal slices from adult male rats, the beneficial effects of sex steroids on CA1 spinogenesis and plasticity depend on rapid activation of multiple cell signaling pathways.

Although similar ex vivo studies have not been conducted in adult female rats, in vivo studies from our laboratory demonstrate that the ability of dorsal hippocampal infusion of E_2 or progesterone to enhance OR and/or OR memory in adult ovariectomized mice depends on numerous cell signaling events in the dorsal hippocampus. E_2's ability to enhance object memory involves rapid activation of multiple cell signaling pathways (ERK, PI3K, PKA, and mTOR), glutamate receptors (NMDA, metabotropic glutamate receptor 1 [mGluR1]), and epigenetic processes (histone acetylation, DNA methylation; Fernandez et al., 2008; Lewis et al., 2008; Fan et al., 2010; Zhao et al., 2010, 2012; Fortress et al., 2013; Boulware et al., 2013). Similarly, progesterone enhances OR and OP in ovariectomized female mice via ERK and mTOR activation and may also involve canonical Wnt signaling (Orr et al., 2012; Fortress et al., 2015). In the case of progesterone, effects on OR and OP are mediated by both intracellular and membrane PRs in the dorsal hippocampus (Fortress et al., 2015). With respect to the role of ERs in E_2-induced cell signaling, both ERα and ERβ enhance OR and OP memory consolidation in ovariectomized mice via ERK activation (Boulware et al., 2013). This activation is accomplished via interaction with mGluR1, suggesting that ERα and ERβ regulate ERK signaling indirectly through glutamate receptors. Although GPER also enhances both OR and OP memory consolidation in ovariectomized mice, it does so by activating c-Jun N-terminal kinase (JNK) instead of ERK and acts in an E_2-independent manner (Kim et al., 2016). Together, this work demonstrates that ERs may regulate memory formation in females via distinct cell signaling pathways. Whether similar pathways are necessary for memory consolidation in adult males is unknown. The fact that ERα, ERβ, and GPER differentially regulate pre- and postsynaptic plasticity in hippocampal slices from adult male and female rats (Oberlander and Woolley, 2016) suggests possible sex differences in how the ERs mediate memory formation. Contextual fear conditioning, another hippocampus-dependent form of learning, differentially regulates ERK phosphorylation in gonadally intact males and females, at least in the ventral hippocampus (Gresack et al., 2009). In this region, but not in the dorsal hippocampus, contextual fear conditioning increases phospho-ERK (both p42 and p44 isoforms) in males but not females (Gresack et al., 2009). This sex difference is associated with enhanced conditioning in males relative to females (Gresack et al., 2009), suggesting learning-induced sex differences in activation of cell signaling. Similarly, another study of gonadally intact mice found that females exhibited impaired fear extinction and substantially less dorsal hippocampal p42 ERK phosphorylation relative to males (Matsuda et al., 2015). Thus, although exogenous E_2 can robustly activate cell signaling in the female hippocampus, endogenous alterations triggered by learning (at least fear learning) may be less substantial than those seen in males. Considerably more work directly comparing the effects of learning and sex steroid hormones on cell signaling in males and females will be necessary to address this issue.

Hippocampally Synthesized Sex Hormones

Finally, it is important to note that the sex steroids that endogenously influence the brain and behavior have traditionally been thought to originate in the gonads. However, increasing evidence from multiple species suggests a critical role for sex steroids synthesized locally in the brain (Kretz et al., 2004; Prange-Kiel et al., 2006; Remage-Healey et al., 2008, 2010; Azcoitia et al., 2011; Bailey et al., 2013). All of the enzymes necessary for sex steroid hormone synthesis are localized within the

hippocampus, including aromatase, the enzyme that converts androgens to estrogens (Hojo et al., 2004; Prange-Kiel et al., 2006; Tabatadze et al., 2014). In female rats, levels of progesterone, estrone, E_2, testosterone, and androstenedione fluctuate in the hippocampus during the estrous cycle such that levels of all but progesterone and testosterone are highest during proestrus (Kato et al., 2013). One report indicates that levels of E_2 and testosterone within the hippocampus are higher in males than in females any stage of the cycle (Kato et al., 2013), whereas other data suggest that hippocampal levels are higher in gonadally intact females than in males (Fester et al., 2012). The functional implications of the putative sex differences are unclear, in that CA1 dendritic spine density is similar in hippocampal slices from gonadally intact males and females (Fester et al., 2012; Kato et al., 2013). In vivo, however, CA1 spine density is higher in gonadally intact female rats than in males (Fester et al., 2012), indicating a significant difference between in vitro and in vivo preparations. In vivo, long-term systemic treatment with the aromatase inhibitor letrozole significantly reduces CA1 spine synapse density in both gonadally intact and ovariectomized female rats, whereas density in males is unaffected (Zhou et al., 2010; Fester et al., 2012). Given that aromatase levels are similar in males and females (Fester et al., 2012; Tabatadze et al., 2014), these data suggest that the hippocampal neurons of females are more sensitive to levels of hippocampal E_2 than those of males. This notion is supported by other in vivo data showing that systemic letrozole impairs LTP and transiently dephosphorylates the actin-binding protein cofilin substantially more in gonadally intact females than in males (Vierk et al., 2012).

These data suggest that reduced aromatase activity might impair hippocampal memory more in females than in males. In humans, variants of the aromatase gene (*CYP19A1*) are associated with Alzheimer's disease in women but not men (Medway et al., 2014), suggesting sex differences in the link between aromatase expression and cognition. Within men, however, a *CYP19A1* allele associated with lower serum E_2 levels is linked to lower bilateral posterior hippocampal gray matter volumes (Bayer et al., 2013) but not to altered emotion, verbal, or spatial memory (Vierk et al., 2015). However, knockout of the aromatase gene in mice results in similar spatial reference memory impairments in gonadally intact males and females (Martin et al., 2003). Thus, sex differences that relate to aromatase gene expression may be limited to certain types of cognition or species. Studies examining the effects of aromatase inhibition on cognition have largely included just one sex, so information on sex differences is limited. Studies in postmenopausal women with breast cancer are somewhat inconsistent, but long-term letrozole treatment reportedly impairs hippocampus-dependent memory and decreases activity in the hippocampus (Bayer et al., 2015). Consistent with this finding, data from our laboratory show that intrahippocampal infusion of letrozole impairs object recognition and spatial memory consolidation in ovariectomized female mice (Tuscher et al., 2016b). Among males, systemic treatment with letrozole impairs memory consolidation in rats (Graham and Milad, 2014). Similarly, intrahippocampal administration of the aromatase inhibitor AID impairs spatial memory in the male zebra finch (Bailey et al., 2013). Together these data suggest that hippocampal E_2 is important for hippocampal memory consolidation in both sexes. However, additional studies are needed to compare directly in both sexes the extent to which de novo hippocampal E_2 synthesis is necessary for hippocampal memory formation.

CONCLUSIONS AND IMPLICATIONS FOR FUTURE RESEARCH

What conclusions might be drawn from several decades of research on sex differences in hippocampal function? With respect to memory, the preponderance of evidence suggests that males outperform females in tests of spatial memory, whereas females outperform males in tests of object memory. We focused on these two types of hippocampus-dependent memory because of the availability of translationally relevant tasks for humans and rodents. To this point, it is important to note that the male advantage in spatial memory and the female advantage in object memory are found in both humans and rodents. Thus, pinpointing the neurobiological bases underlying mnemonic sex differences in rodents will likely provide important insights into mnemonic sex differences in humans. A key element to this endeavor will be to understand the developmental etiology of sex differences in hippocampal memory. Sex differences in spatial memory appear to be organized in early development by sex steroid hormones. Although it is unclear whether the effects of sex steroids at puberty are organizational or activational in nature, they do appear to significantly mediate spatial memory in both adolescence and adulthood (Fig. 6). Hippocampally derived sex steroid hormones may also play an important role in early development and adulthood (Fig. 6), although it is not yet clear whether the contributions of local steroids differ from those of gonadally derived steroids. It is also worth noting that the hippocampus mediates other types of learning and memory that have not been discussed in detail here. For example, sex differences favoring males are observed in contextual fear conditioning and fear extinction (Maren et al., 1994; Gresack et al., 2009; Matsuda et al., 2015). Given that women are at a higher risk of anxiety disorders, including posttraumatic stress disorder (Breslau et al., 1998; Pigott, 2003), understanding the nature of sex differences in fear learning may provide important insights for the prevention and treatment of these disorders in women.

During both adolescence and adulthood, sex differences are observed in numerous aspects of hippocampal morphology and function, including dendritic branching and spine density, neurogenesis, and LTP. In adolescence, more dendritic pruning may occur in the female hippocampus, as it does in other cognitive brain regions, and, although a loss of dendritic spines occurs in the

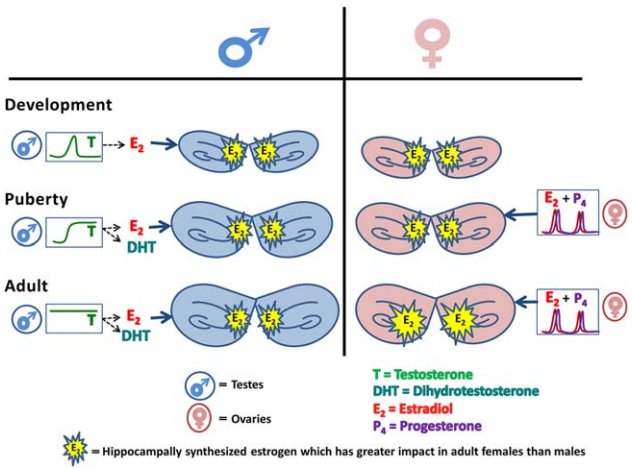

Fig. 6. Schematic diagram illustrating the effects of sex steroid hormones on the hippocampus during development, puberty, and adulthood. In development, testosterone (T) masculinizes the male hippocampus via its aromatization to estradiol (E_2). During puberty, the female brain becomes exposed to cyclic fluctuations of E_2 and progesterone (P_4) in which E_2 levels peak prior to ovulation and P_4 levels peak just after ovulation. In males, testosterone levels rise during puberty and remain elevated in a diurnal cycle throughout adulthood. Hippocampally synthesized E_2 is present in both males and females but has more of an impact on hippocampal function in adult females than in adult males.

hippocampus of both sexes, spine loss appears to be regulated by gonadal hormones only in males (Meyer et al., 1978; Yildirim et al., 2008; Chowdhury et al., 2014). Whether these sex differences in maturation during the adolescent period contribute to sex differences in hippocampal memory formation remains unknown, so much more work is necessary to appreciate how developmental sex differences influence those observed in later in life. In adulthood, sex differences in dendritic measurements are inconsistent and may be obscured by cyclic hormone fluctuations. For example, proestrus female rats exhibit greater CA1 dendritic spine density and DG cell proliferation than males or females in other stages of the cycle (Tanapat et al., 1999; Shors et al., 2001). However, when males and females are compared regardless of the cycle, few differences are observed (Gould et al., 1990a; Markham et al., 2005; Salas-Ramirez et al., 2010; Bowman et al., 2015; Duarte-Guterman et al., 2015). Females in proestrus also have facilitated LTP relative to males or females in other estrous stages (Warren et al., 1995; Good et al., 1999), however, differences favoring males have been observed when the cycle was not taken into account (Maren et al., 1994; Maren, 1995; Yang et al., 2004). Finally, few if any studies have directly examined sex differences in cell signaling, so this is an area ripe for future investigation.

It can be difficult to draw broad conclusions about sex differences in hippocampal memory because they appear to vary based on species, strain, and age and to depend on several aspects of experimental design. Across studies of young adult rats, a relatively consistent male advantage is observed for spatial reference memory tested in the Morris water maze (Jonasson et al., 2005). Male rats and mice appear to maintain intact spatial reference memory in the water maze until after middle age, as suggested by reports that sex differences favoring males observed in middle age disappear in old age as a result of age-related deterioration in males (Markowska, 1999; Frick et al., 2000). As with the water maze, a robust male advantage for spatial working memory in the radial arm maze is observed in young adult rats that appears to be resistant to changes in the testing or housing environment (Seymoure et al., 1996). Consistent with sex differences favoring males in the water maze and radial arm maze, male advantages are typically reported for the OP task in both rats and mice (Luine et al., 2002; Luine, 2002; Frick and Gresack, 2003; Salas-Ramirez et al., 2010; Bowman, 2005; but see Benice et al., 2006). In contrast to the spatial tasks, there is no clear consensus about the existence of sex differences in OR in rats or mice. In humans, the picture is even more complex. Robust sex differences favoring males are observed in the virtual Morris water maze that appear prior to puberty and persist into old age (Moffat et al., 1998; Astur et al., 1998, 2004; Sandstrom et al., 1998; Driscoll et al., 2005; Burkitt et al., 2007; Woolley et al., 2010; Nowak and Moffat, 2011; Nowak et al., 2014). However, studies using virtual radial arm mazes show no sex differences in performance (Astur et al., 2004; Levy et al., 2005). Moreover, women tend to notice object substitutions and displacements more than men (Silverman and Eals, 1992; Eals and Silverman, 1994; McBurney et al., 1997; Levy et al., 2005), which would appear inconsistent with rodent findings from OR and OP. However, as noted above, it is unclear how well performance in two-dimensional object array tasks maps onto landmark use in navigation tasks. Although the aforementioned summary of sex differences in hippocampal memory among humans and rodents provides some general conclusions about this literature, it is important to remember the discrepant findings mentioned above. The field would greatly benefit from additional studies with more standardized protocols across laboratories to determine the effects of sex and/or gender on various forms of hippocampal memory from the juvenile period through old age.

Although sex differences in cognitive function have been documented for decades, our knowledge of the biological bases underlying these differences remains relatively rudimentary. Much more research is needed to understand more fully the etiology of sex differences in memory and other cognitive functions. We hope that the recent NIH policy mandating the consideration of sex as a biological variable in grant applications stimulates the collection of exciting new data to fill the gaps. Such data could have significant benefits for the mental health of both men and women. According to one analysis that measured the worldwide burden of mental and substance abuse disorders in terms of disability-adjusted life years, boys aged 10 years and under were found to bear a greater burden than girls, whereas women at age 15 years and

older bear a greater burden than men (Whiteford et al., 2013). The increased burden for boys during childhood likely is due to the higher incidence of childhood behavioral disorders among boys (e.g., autism-spectrum disorders, attention deficit-hyperactivity disorder; Whiteford et al., 2013; Keshavarzi et al., 2014; Christensen et al., 2016). The increased burden in women likely results from greater prevalence, progression, and/or severity of conditions such as anxiety and mood disorders, schizophrenia, and Alzheimer's disease (Launer et al., 1999; Pigott, 2003; Kessler et al., 2005; Gillies and McArthur, 2010). Women also exhibit greater use of and dependence on cocaine than men (Lejuez et al., 2007) and have worse functional outcomes after stroke (Reeves et al., 2008). These examples are by no means an exhaustive accounting of sex differences in the prevalence and symptomology of various mental illnesses but are simply meant to illustrate the existence of such differences. Understanding why men and women differ in susceptibility to various mental disorders will require far greater insights into how the brains of males and females differ at baseline and in response to stimulation, exercise, stress, injury, aging, and other perturbations. The attention devoted to sex differences in this special issue is a great step in the right direction to stimulate the generation of many new findings.

ACKNOWLEDGMENTS

The authors thank the University of Wisconsin—Milwaukee College of Letters and Sciences for their support as well as Jaekyoon Kim, Lisa Taxier, and Jennifer Tuscher for critical comments on the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors have no known or potential financial or personal conflicts of interest.

ROLE OF AUTHORS

Both authors contributed equally to the conceptualization and writing of this Review.

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