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Sex Hormones and Cognition: Neuroendocrine influences on memory and learning.

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Androgens, estrogens and cognition in adulthood

Abstract

Sex differences in neurological disease extend from incidence, severity, progression and symptoms and may ultimately influence treatment. Cognitive disturbances are frequent in neuropsychiatric disease with men showing greater cognitive impairment in schizophrenia, but women showing more severe dementia and cognitive decline with Alzheimer's disease. Although there are no overall differences in intelligence between the sexes, men and women demonstrate slight but consistent differences in a number of cognitive domains. These include a male advantage, on average, in some types of spatial abilities and a female advantage on some measures of verbal fluency and memory. Sex differences in traits or behaviors generally indicate the involvement of sex hormones, such as androgens and estrogens. We review the literature on whether adult levels of testosterone and estradiol influence spatial ability in both males and females from rodent models to humans. We also include information on estrogens and their ability to modulate verbal memory in men and women. Estrone and progestins are common components of hormone therapies, and we also review the existing literature concerning their effects on cognition. We also review the sex differences in the hippocampus and prefrontal cortex as they relate to cognitive performance in both rodents and humans. There has been greater recognition in the scientific literature that it is important to study both sexes but also to analyze study findings with sex as a variable. Only by examining these sex differences can we progress to finding treatments that will improve the cognitive health of both men and women.

Introduction

There is a need for a better understanding of how sex differences may inform the research and medical community on disease incidence, manifestation, and treatment (92, 111, 413). Highlighting sex differences in research can have clinical relevance for understanding risk, manifestation, and treatment efficacy of diseases that are more often observed in one sex versus the other. For example, there are sex differences in the likelihood of developing neuropsychiatric and neurodegenerative disorders that commonly involve cognitive difficulties, including depression, schizophrenia, and Alzheimer's disease (10, 39). Women are more than twice as likely as men to develop depression (233, 263), are three times more likely to be diagnosed with Alzheimer's disease, and experience greater cognitive deterioration as Alzheimer's disease progresses (100, 241, 290, 554). In contrast, men are at greater risk for developing schizophrenia (10) and have greater cognitive impairment associated with schizophrenia compared to women (216, 375). Estrogens and androgens are implicated in risk and symptomatology of these

disorders (39, 265, 562). The cognitive impairments of these disorders are accompanied by reduced integrity of the hippocampus and prefrontal cortex, and thus our review will focus on the role of sex steroids on these regions in adulthood.

Although some researchers have indicated that the study of sex differences in cognition may be a precarious slope it is important to note that there are no differences in overall intelligence between the sexes (243, 301). However, men and women demonstrate slight but consistent differences in a number of cognitive abilities. Among the largest sex differences in cognitive tasks are a male advantage on some visuospatial tasks and a female advantage on certain verbal tasks (242, 286, 396, 636); see Figure 1). Smaller differences in performance between the sexes are observed in other domains, such as a female advantage in perceptual speed (259, 396). Intriguingly there are also sex differences in rodents and non-human primates favoring males for spatial ability and in females for skilled motor tasks (282, 309, 356, 358). These sex differences in certain cognitive tasks suggest that early (organizational) or late (activational/adult) effects of sex hormones are involved. Thus studying sex differences in cognition is important to understand the origins of sex differences in the cognitive manifestations of diseases such as Alzheimer's and schizophrenia as noted above. The organizational effects of estrogens and androgens on cognition are beyond the scope of the review and the reader is directed to other reviews on the subject (58, 272, 412, 642). This review highlights the role of estrogens and androgens in adulthood in modulating cognitive functions that show sex differences in performance in mammals, including both humans and rodents.

Sex differences in the Central Nervous System

The effects of sex steroids on the adult brain and cognition occur in the context of organizational sex differences in the central nervous system, which develop through an interaction between exposure to sex steroids and genotype during ontogeny (24, 25, 217). Sex differences are evident in the size of certain brain structures, the organization of the central nervous system (CNS), and in neurotransmitter receptor number and distribution. A detailed explanation of all sex differences in CNS is beyond the scope of this review and the reader is directed to excellent reviews on the subject (116, 217, 542). A recent meta-analysis indicated that, on average, total brain size is larger in men than in women by approximately 11%, and men have larger absolute grey matter and white matter volumes (536). However, females have a greater proportion of grey matter to white matter than men (11, 232). Sex differences in brain volume cannot be fully accounted for by differences in body size (e.g., (11, 116), although there is controversy on how to appropriately control for physical differences between the sexes. A meta-analysis indicates that absolute (i.e., not correcting for body size or total brain volume) sex differences exist in specific brain regions (536). These include larger volumes of the hippocampus and amygdala in men and larger volumes of areas associated with auditory and verbal perception (e.g., Heschyls gyrus and the planum temporal) in women (536). However, sex differences in volumes of specific brain structures are often equivocal and depend on whether, and what kind of, correction factor is applied (e.g., total intracranial volume, body size, or head size (519). The women-favoring volume differences in language-associated areas hold even when controlling for differences in brain size (251, 295, 553, 667). On the other hand, relative to brain size or intra-cranial volume, women have either larger hippocampi (169, 210, 451) or no significance difference in hippocampal volume compared to men (88, 294, 363, 446, 507, 609). These equivocal results may, in part, stem from a failure to consider sexual dimorphisms within certain sub-regions of the hippocampus (487), or, and perhaps more likely, a failure to control for age, exercise, body mass index, and education as these all influence hippocampal volume (161, 459, 518, 520). It should also be recognized that methodological differences among studies may contribute to differences in findings (324). The anterior and posterior hippocampi have different functional connectivity, leading to hypotheses that they are preferentially activated during different forms of encoding and retrieval (452, 499). Persson et al. (487) found that women specifically have larger posterior, but not anterior, hippocampi than men, and found that these regions may also have different structural connectivity between the sexes. Finally, other influences unique to the female physiology, such as menstrual cycle phase (506) and reproductive experience (46, 48,

482, 483) may also contribute to differences in hippocampal volume in women, factors that are not always controlled for in studies.

Perhaps necessitated by smaller overall brain size in women compared to men (597), women show greater overall cortical connectivity as measured using magnetic resonance imaging tractography (218) and voxel-wise mapping of local functional connectivity density (611). Furthermore, analysis of structural connectomes in males and females, computed using diffusion tensor imaging, found greater interhemispheric connectivity in females and greater within-hemispheric connectivity in males (289), even into older age (486). Interestingly, cognitive performance is more strongly correlated with white matter volume in women than in men (232), suggesting that women may make more efficient use of white matter. In addition, studies have demonstrated that women have higher cerebral blood flow compared to men during both rest and cognitive activity (See (542) for a review). Clearly there are a number of sex differences in connectivity and activity patterns that may be related to differences in cognitive function in men and women. In many ways, this field is in its infancy as researchers are gaining knowledge of how to correct for brain/body size, age, experience, exercise and reproductive factors that may affect the size and appearance of sex differences in the brain. While this is by no means an exhaustive account of sex differences in the central nervous system, this brief summary is a reminder that the effects of sex hormones in adulthood occur in the context of numerous differences between the average male and female brain. Some have argued that observed sex differences in behavior or brain can only be appropriately termed sex differences when organizational effects of hormones are involved (414). However others argue that, regardless of the organizational component, sex differences can inform whether variations are qualitative, quantitative, population-based or may result from differences in underlying neural mechanisms (54). The next section of this review discusses sex-favoring cognitive abilities, and subsequent sections will review evidence that these abilities are hormonally-modulated by sex steroids in adulthood.

Female-favoring Abilities in Cognition

Verbal Memory and Fluency

On average, women are better at recalling words from spoken lists (e.g., (655) and acquiring verbal paired associates than men (e.g., (202, 613). These sex differences emerge before puberty (e.g., (343) and last into older age (e.g., (266, 366). As will be reviewed more fully in subsequent sections, observed differences in performance in adulthood also reflect activational/adult influences of sex steroids. Adult levels of estrogens and progesterone are related to performance on verbal memory and fluency, as hormone therapy (HT) improves verbal memory in postmenopausal or surgically menopausal women (146, 314). Furthermore, differences in verbal fluency performance can be seen across the menstrual cycle, with high estrogens associated with better performance and low estrogens during the menses phase associated with poorer performance both within and between subjects (244). The left medial temporal lobe (including the hippocampus) and the prefrontal cortex are involved in, and correlate with, performance on verbal learning tasks including the California Verbal Learning Task (CVLT) and Narrative Recall tasks (182, 308). The left medial temporal lobe is selectively activated during processing of novel but not familiar words in an fMRI task (225, 493, 549) and cued recall tasks (594). Hippocampal sclerosis, a condition characterized by neuronal loss in the hippocampus, is associated with impaired performance on verbal paired associate learning and immediate and delayed recall of passages (544). Among individuals with excisions in the temporal lobe for treatment of epilepsy, verbal memory impairment correlates with the density of hippocampal pyramidal cell density in the CA3 region (547). Further, the size of the anterior hippocampus is positively correlated with verbal memory in nondemented elderly individuals (235). Together, these studies implicate the left hippocampus and prefrontal cortex in acquisition, retention, and retrieval of information in long-term memory in adulthood and later life. Despite these findings, the neural underpinnings of the sex difference in verbal memory are not yet clear. Sex differences have been noted in brain activation in response to these tasks, with activation differences during encoding and retrieval noted in both the hippocampus (549) and prefrontal cortex (308). Berenbaum (57) found that partial resection of the left hippocampus to treat seizures impaired

both men and women's performance on subtests of the CVLT similarly. However, women performed better than men both before and after surgery, indicating the sex differences were not likely a result of hippocampal dysfunction. Instead, the female advantage correlated with prefrontal cortex-mediated encoding strategies (57). Thus, the female advantage in verbal memory could stem from efficient prefrontal cortex-mediated encoding rather than, or in addition to, hippocampal integrity.

Women also have an advantage in some forms of verbal fluency. Verbal fluency tasks require subjects to name as many words as possible beginning with a certain letter (phonemic fluency) or belonging to a specified semantic category (semantic fluency). Verbal fluency is considered an executive task as it requires focused attention, choosing a search strategy, and maintaining and manipulating information in working memory (377). The strategy of switching between clusters of related words is mediated by the prefrontal cortex (615). Verbal fluency also recruits episodic memory, and the generation of words within a semantic or phonemic category is associated with temporal lobe functioning (615). Accordingly, phonetic fluency preferentially activates the left frontal cortex (122, 183) and is impaired by frontal lobe lesions (484, 615). In contrast, semantic fluency is associated more strongly with activation of the left temporal lobe (449, 481) and is more intensely affected by temporal lobe damage (e.g., (37, 273, 440, 457). Women have a more reliable advantage in phonemic fluency than semantic fluency when compared to men (e.g., (75, 120, 654, 655). Additionally, women's advantage in verbal fluency is related to use of prefrontal cortex-related strategy of switching clusters frequently (57, 339, 655). Thus, the prefrontal cortex appears to contribute to females' advantage in specific language tasks beyond or in addition to the sex differences in intra and inter-hemispheric connectivity and regional volume differences already discussed.

Research using fMRI (566) has found sex differences in frontal activation during language tasks. Specifically in phonological tasks, brain activation in men is lateralized to the left inferior frontal gyrus, but the pattern of activation in women is more diffuse and involves both the left and right inferior frontal gyrus (Broadmann areas 44 and 45, part of the dorsolateral prefrontal cortex) (566). The sex difference in lateralization of activation did not extend to semantic or orthographic category tasks. Unfortunately, this study did not track menstrual cycle activity, as activation patterns during semantic retrieval (338), mental rotation (135, 558), and other tasks (e.g.,(506) are influenced by the menstrual cycle and should be considered when studying brain activation. Similarly, activation during verbal fluency may also be influenced by the menstrual cycle. While Halari et al. (238) found similar brain activation in men compared to women tested during menses (a point in the menstrual cycle when estradiol is low), women during the midluteal or preovulatory surge (when estradiol levels are higher) perform better on tests of verbal fluency than women during the menses phase. Thus, while verbal fluency relies on the coordinated activity of both the frontal and temporal lobes, women appear to have a particular advantage in phonological verbal fluency and processing compared to men, and this is related to use of prefrontal cortex-mediated strategies and differential prefrontal cortex activation.

Male-favoring Abilities in Cognition

Aspects of Spatial Memory

Spatial memory is a multifaceted cognitive function that requires the ability to encode, store, and retrieve spatial information about routes, locations, or spatial layouts. It requires coordination among the components of a complex circuitry that includes the hippocampus, prefrontal cortex, parietal cortex, striatum, and visual system (669). Particular aspects of spatial cognition, and thus different behavioral tasks, preferentially recruit different components of this circuitry. Spatial memory can be further classified as either spatial working memory or reference memory. Working memory is the active processing of trial-unique information to guide prospective action (32) and requires the shorter-term storage and manipulation of changing information to complete the task. Reference memory, however, involves long-term storage of information that remains stable over time (465). There is evidence for a neural basis in mediating the distinction between spatial reference versus working memory, as spatial reference memory relies on the hippocampus and caudate nucleus (476) whereas spatial working memory recruits and requires the integrity of the hippocampus and prefrontal cortex (33, 687). Additionally, there is a neural

distinction between allocentric (absolute, viewpoint-independent, map-like) versus egocentric (viewpoint-dependent, response- or cue-based) representations of spatial layouts. The hippocampus and retrosplenial cortex selectively mediate allocentric spatial navigation (136, 287, 668), whereas the dorsal striatum selectively mediates egocentric spatial navigation (136, 417). Individuals using an allocentric strategy in a virtual navigation task show greater activation in the hippocampus, parahippocampal region, and thalamus compared to individuals who use an egocentric strategy (312). Furthermore, hippocampal damage in humans is associated with deficits in allocentric but not egocentric spatial memory (279, 280). This is not an exhaustive taxonomy of aspects of spatial cognition but serves to highlight that spatial memory is not a unitary construct. Different aspects of spatial memory preferentially recruit different brain structures, including the hippocampus and prefrontal cortex.

Males have Specific Advantages in Spatial Cognition

As mentioned above, meta-analyses indicate that men, on average, perform better than women on a number of spatial tasks, such as spatial perception tasks and mental rotation (378, 636) . Additionally, men outperform women, on average, in a simple spatial discrimination task in which an angled line must be correctly matched to its counterpart with the same angle among an array of lines (379). Men also outperform women, on average, in measures of mental rotation where a mental representation of a two- or three-dimensional object must be mentally manipulated to find the correct rotated version of the object (491). Performance in mental rotation tests correlates with performance in a navigational task (194, 437, 548, 577). Indeed, across a number of species males have an advantage in spatial navigation tasks compared to females (309). For example, men outperform women in virtual and real-world maze and navigation tasks (28, 194, 288, 403, 437, 545, 548, 577, 678). Of course, some studies in humans have not found sex difference in performance in radial arm mazes (28, 376) unlike in rodents (see (309). However, other studies suggest that availability and number of landmarks within a task influences whether sex differences are observed (19, 194) and as noted above meta-analyses indicate sex differences favoring men on these types of spatial tasks overall (378, 636). Spatial navigation can be assessed in rodents using the Morris Water Maze task, in which subjects must learn the location of a submerged platform over repeated trials by navigating using extra-maze cues located throughout the testing room (443). The standard version of the Morris Water Maze assesses reference (hippocampus-dependent) memory by keeping the platform location in a constant quadrant throughout testing (634) (see Figure 2). Male voles, mice, and rats outperform female conspecifics in learning the location of a hidden platform (110, 193, 309), but do not show better memory for the target quadrant once the knowledge has been acquired (110, 193). Indeed, while not covered by this review it is important to note that aspects of spatial memory are organized developmentally by exposure to sex hormones, as performance on the radial arm maze is masculinized in females neonatally given estradiol benzoate or testosterone, and neonatally castrated males perform similarly to females when tested as adults (529, 660, 661). Generally, sex differences favoring males are observed in spatial learning when estrogens are high in females (190, 193), implicating a role of estrogens and possibly progestins, in adulthood in the modulation of spatial performance in female rodents. Adult effects of sex steroids on spatial learning and memory will be reviewed further in subsequent sections.

It is important to be aware that spatial tasks differ in their working memory demands and aversiveness, and these factors may be important in the observed sex differences. Jonasson et al. (309) conducted a meta-analysis of Morris Water Maze and Radial Arm Maze studies in rats and mice. In rats, there is a male advantage both in reference spatial memory and working spatial memory tasks. Importantly, however, the male advantage is reduced by pre-training and group housing, factors that reduce stress differentially between the sexes (55, 656). The male advantage was particularly great when working and reference memory demands were combined within a single task, as in the case of certain radial arm maze designs (309). Thus, stress, task demands, landmark use and hormone levels (discussed below) are all likely to affect sex differences in spatial learning and memory, and should be considered when interpreting results from investigations of sex differences.

It is also important to note that not every aspect of spatial ability or memory favors males and a notable exception is object location memory. Silverman and Eals (578) demonstrated that

women outperformed men in the memory for object locations within a spatial array. More recently, a meta-analysis has found that women have a small to intermediate advantage in object location memory under a variety of testing conditions (635). Similarly, women have an advantage in a working memory task requiring memory for object-place associations compared to men (147, 376). Female rodents also outperform males in object placement tasks (185, 640), which rely on the hippocampus and prefrontal cortex (158, 448).

The male favouring sex difference in spatial ability across a wide variety of species lends itself to an interpretation from an evolutionary perspective. Evolutionary theorists (149, 200, 568) have posited that male and female superiority in spatial navigation and object location memory, respectively, stem from a division of labor of men as hunters and females as foragers in our environment of evolution. Spatial navigation skills, it is thought, evolved in males to support the ability to range far from home in search of prey. In contrast, women may have evolved better object location memory to support the ability to forage for items (e.g., berries, plants) within visual arrays. Unlike spatial navigation, memory for object location can be encoded without reference to a complex topographical representation of an environment. The encoding of object locations within different frames of reference (egocentric, allocentric) have different neural underpinnings (114). Thus, spatial memory is a multidimensional set of abilities, and the male advantage in spatial cognition is specific to certain aspects of spatial cognitive ability.

Males and females also employ different spatial strategies, on average. In both humans and rodents, males are more likely to use a hippocampus-dependent allocentric strategy to navigate compared to females, who are more likely to use an egocentric, dorsal striatum-dependent strategy. Dorsal striatum-dependent strategies include use of local landmark cues or response sets (e.g., “turn left at the intersection;” (194, 432, 660). Female rodents perform equivalently to male rodents in cued versions of the water maze where the most efficient strategy is to use a response-based (egocentric) approach (530). However, among both rodents and humans that use a place strategy (allocentric) to navigate, males have significantly better performance than females (548, 624). These results suggest that males may also be able to use a spatial strategy more efficiently than females (194, 624). Perhaps related to different selection and/or efficiency of navigation strategies, neuroimaging studies have shown sex differences in brain activity pattern during virtual navigation tasks (231) and other male-favoring spatial tasks. For example, Gron et al. (231) found greater activation in the left hippocampus in men relative to women during virtual navigation, and increased right parietal and prefrontal activity in women relative to men. Women and men exhibit different cortical activation patterns during mental rotation tasks even in the absence of performance differences (284). Males show predominantly parietal activation while females additionally show inferior frontal activation (284, 654). Sex differences in spatial strategy are partly a result of the organizational effects of androgen exposure (see below and (660) and females with increased endogenous androgen exposure during development have an advantage in spatial tasks (59, 245). However strategy differences are also seen in females across the estrous cycle (341, 537), with perhaps paradoxically, females showing more use of spatial strategies during proestrus, a time when estradiol levels are high.

Thus, there are sex differences in specific aspects of spatial and verbal memory, and these functions recruit the prefrontal cortex and hippocampus to varying degrees. Whenever sex differences are observed, sex hormones are a likely contributor to the observed differences. In addition to their role in regulating reproductive behaviors, estrogens and androgens have important roles in cognition. The remainder of the review will therefore integrate human and non-human animal findings regarding the role of estrogens and androgens in sex-favoring hippocampal and prefrontal cortex functioning across the adult lifespan.

Hippocampus

Hippocampal Anatomy

The hippocampal formation is located in the medial temporal lobe and contains a number of different lamellae (16). This region contains a multitude of cellular phenotypes with the most conspicuous being the pyramidal neurons of the CA1, CA2, and CA3 layers located in the hippocampus proper, and the granule neurons located in the granule cell layer of the dentate gyrus (reviewed in (20). Input to the hippocampus arises from multiple levels of the entorhinal

cortex, which sends direct afferents to the dentate gyrus, CA1, and CA3. However, based on electrophysiological and tract tracing studies, these distinct layers are linked via a unidirectional circuit in which granule neurons send excitatory projections to pyramidal neurons in the CA3 region, which in turn, send excitatory inputs to pyramidal neurons of the CA1 region (See Figure 3). This "trisynaptic circuitry" is very similar in structure across a number of different mammalian species, including humans (419), and is thought to be important for the flow of information to the cortex for memory storage, as discussed below**.**

Hippocampal Function

The hippocampal formation has long been recognized as a structure important for memory (Cross reference: Memory: anatomical organization of candidate brain regions; Memory: neural organization and behavior). In 1957, Scoville and Milner first described patient "H.M.' a man who lost the ability to form declarative, but not non-declarative memories after bilateral removal of the medial temporal lobe, including the hippocampus (559, 593). It has since been established that this limbic structure has a critical role in episodic memory for spatial, contextual, and relational information (153). Hippocampal lesions produce spatial reference memory deficits in humans (429, 461, 586) and rodents (328, 666). Lesions to the dorsal but not ventral hippocampus impair spatial reference acquisition in rodents (502), suggesting that the dorsal hippocampus in rodents may play the greater role in reference memory. As previously discussed, spatial working memory requires the prefrontal cortex and the hippocampus (33, 687), and lesions to either region reliably produce impairment in spatial working memory (38, 466, 666). It is important to re-iterate that functional connectivity across brain regions (e.g., (289), and regions of the hippocampus (487) may differ between males and females. However, in rodents, the dorsal hippocampus may be more associated with reference spatial memory (502), whereas spatial working memory is affected by manipulations of both the dorsal hippocampus (502) and the ventral region of the hippocampus, from where hippocampal projections to the prefrontal cortex originate (115, 228, 297, 299, 598, 629). Notably, the dorsal hippocampus of rodents is equivalent to the posterior hippocampus of primates (596). For example, the posterior region of the human hippocampus is activated during retrieval of an allocentric cognitive map (136, 143, 287). In this regard, it is intriguing that London taxi cab drivers, who undergo years of extensive spatial training to learn the intricate streets of London, England show growth in the posterior, but not anterior, hippocampus (400). This may be analogous to the larger hippocampal volumes seen in food caching birds compared to non-food caching birds (344, 570). The reader is directed to several reviews dedicated to the relation between hippocampal volume and spatial ability (569, 686).

The role of the hippocampus is not limited to spatial cognition, and the integrity of the hippocampus is important in episodic and contextual memory as well as pattern separation and completion (153). For example, as previously reviewed, the hippocampus is also implicated in learning verbal information (182). The hippocampus also plays a role in encoding of context during contextual fear conditioning in humans and rodents (14, 497) and pattern separation and completion (36, 327). Furthermore, the hippocampus is also well known for its involvement in stress reactivity and contains the highest concentration of glucocorticoid receptors in the brain (133, 296, 420). In particular, the rodent ventral hippocampus is thought to be an important modulator of stress and anxiety (167). As previously discussed (e.g., (289), intra- and inter-hemispheric functional and anatomical connectivity differs between the sexes. Further, hippocampal activation during navigational and verbal memory tasks differs between the sexes (231, 566) and across the menstrual cycle in women. Thus, there are likely to be sex differences in the functions and properties of the hippocampus, and its interactions with other structures such as the prefrontal cortex, that are not currently fully understood. Interestingly, the adult mammalian hippocampus produces new neurons and glia on a daily basis (as discussed in the next section). Neurogenesis, in particular, is a special form of hormonally mediated structural plasticity and contributes to some forms of hippocampal functioning (see below, (112, 587).

Adult Hippocampal Neurogenesis

In the adult mammal brain, new neurons are generated from precursor cells primarily in two regions: the subventricular zone (SVZ) around the walls of the ventricles and the subgranular

zone (SGZ) adjacent to the granule cell layer in the dentate gyrus of the hippocampus (see (460) for a description in avian species). Cells generated in the SVZ migrate along the rostral migratory stream to the olfactory bulb, where they mature to become interneurons and integrate into the local circuitry. The germinal layer in the dentate gyrus produces daughter cells that develop into either neurons or glia (15). The identification of newly born cells in the adult brain is facilitated by a number of cellular markers. When administered, the synthetic analogue of thymidine, bromodeoxyuridine (BrdU), is taken up by cells undergoing DNA synthesis during S phase of mitosis and is used to label newly proliferated cells (605). Because BrdU cannot determine the phenotype of newly generated cells, a combination of BrdU and a glial (such as glial fibrillary acidic protein) or neuronal (such as NeuN) marker is used to determine whether the new cell is glia or neuron, respectively. An exhaustive characterization of markers utilized to examine neurogenesis is beyond the scope of this review and the reader is directed to (631) for further information.

Adult hippocampal neurogenesis is divided into several different stages. Dividing progenitor cells in the SGZ give rise to daughter cells during the proliferation phase. Daughter cells then migrate to the granule cell layer and differentiate into either neurons or glia. Once cells have migrated to the appropriate position, neurons extend axons to their targets in the CA3 subregion of the hippocampus and elaborate their dendrites in order to integrate into the local circuitry. Manipulating one or more of these stages can change the overall rate of neurogenesis. The length of time between injection of an exogenous marker and tissue collection can give information regarding different stages of neurogenesis. For example, if the hippocampus is examined 24 hours or 1 month after BrdU injections, one can determine if labeled cells are newly proliferated or are cells that have survived and integrated, respectively. There are also a number of endogenous markers that can be utilized to determine the characteristics of adult-generated hippocampal cells. Ki67 is a nuclear protein that can be detected during all phases of the cell cycle except G_0, suggesting this can be used as an exclusive proliferation marker (204, 555). Another marker, doublecortin (DCX), is a microtubule-associated protein that is expressed in migrating and immature neurons between one to twenty-one days after proliferation in the dentate gyrus (85). It should be noted that merely increasing the number of new neurons may not necessarily be related to better memory as these new neurons may not have been incorporated properly (reviewed in (691)). For example, seizures increase neurogenesis but are associated with detriments to cognition (303), and Alzheimer's disease is associated with increased neurogenesis at certain early stages of the disease, perhaps partly as a compensatory mechanism (305). In addition, neurogenesis-increasing treatments following training promote forgetting of recently learned information (9). Thus, increased neurogenesis in the hippocampus is not universally beneficial or indicative of improved cognition.

Prefrontal Cortex

The prefrontal cortex, the cerebral cortex covering the anterior part of the frontal lobe, is not anatomically or functionally uniform but instead is a collection of inter-related neocortical regions. Traditionally, the prefrontal cortex is considered to include Broadmann areas 8-11 and 44-47. Together, these regions are involved in higher-order cognitive and emotional processes including goal-directed behavior, self-monitoring, decision-making, and impulse-control. These regions have extensive reciprocal connections with many subcortical structures, including the hippocampus, hypothalamus, and amygdala, and communicate with many cortical sensory and motor systems (189). The human prefrontal cortex is broadly divided into dorsolateral, orbitofrontal, and anterior cingulate regions (189) although nomenclature is not universal and there are many functional and anatomical subregions within these broader regions. While there is overlap and coordination in function among the different subdivisions of the prefrontal cortex, the subdivisions are thought to have different roles in specific cognitive and emotional processes (40, 41, 175) and have different anatomical connections to associated regions (227, 228, 621).

The prefrontal cortex is thought to be responsible for 'umbrella' functions, including attention, executive functions, memory retrieval and encoding strategies, as well as effortful decision-making (189, 427) required for many behaviors. The prefrontal cortex's role includes organizing encoding and retrieval strategies that determine input to and output from the

hippocampus (163). For example, successful retrieval of memory is prefrontal cortex-dependent (264, 315). Both short-term/working memory and long-term memory encoding and retrieval are associated with bilateral prefrontal activity in the ventrolateral and dorsolateral prefrontal cortex (dlPFC; (513). Lesion, electrophysiological, clinical, and fMRI studies support the role of the prefrontal cortex in short-term working memory, including but not limited to hippocampus-dependent spatial working memory (113, 117, 410, 411, 470-473, 480, 493, 585). Spatial tasks that involve a short-term working memory component of tracking previous locations involve the medial prefrontal cortex (mPFC; (311).

In humans, dlPFC damage is associated with deficits in executive functioning, including monitoring/planning of behavior and working memory. In contrast, damage to the orbitofrontal cortex is more strongly associated with a lack of inhibition over socio-emotional behavior, and relatively spared cognitive abilities (22). There are organizational differences in the prefrontal cortex between rodents and primates (337, 621) to the extent that some researchers contest the use of the term 'prefrontal cortex' in reference to the anterior portion of the frontal lobe in rodents. It does appear, however, that the rodent "prefrontal cortex" (for lack of a better term) may be subdivided into regions that are functionally homologous to the human dlPFC, anterior cingulate, and orbitofrontal prefrontal cortex (OFPC; (337, 621). The primate dlPFC and anterior cingulate cortex (ACC) are thought by some to have a rodent equivalent within the mPFC, whereas the OFPC may have a homolog in the lateral orbital region of the rat prefrontal cortex (337, 561, 621). Lesions to the mPFC and lateral orbital region in rats cause behavioral changes in rats that are similar to the effects of lesions to the dlPFC and OFPC in primates (337). For example, dlPFC lesions in primates and mPFC lesions in rats impair working memory function (434). Anatomical connections lend some support to this taxonomy of "prefrontal cortex" subdivisions. For example, both the human dlPFC and rodent mPFC are innervated by the mediodorsal nucleus of the thalamus and project to the dorsal striatum, nucleus accumbens, and ventral tegmental area (86, 227, 467). The rodent mPFC can be subdivided into the anterior cingulate cortex, the prelimbic cortex (dorsal) and the infralimbic (ventral) cortices, and these subregions have functional dissociations (213, 260, 627). The infralimbic region is associated with regulation of visceral and autonomic activity, whereas the prelimbic area is more closely associated with limbic-cognitive functions, similar to the human dlPFC (627). Prelimbic and infralimbic cortices have been implicated in working memory (212, 511) and in the stress response, often in an opposing manner. For example infralimbic is excitatory and prelimbic is inhibitory to stress (reviewed in (267). Thus, much like the hippocampus, it is important to keep in mind that different regions of the prefrontal cortex may be involved in regulating different processes, particularly stress and cognition; Complicating matters further, stress can affect cognition in a sex-dependent manner (see (76) for a review).

Interactions Between the Prefrontal Cortex and Hippocampus

There are functional connections between the hippocampus and prefrontal cortex and no task can be said to be purely hippocampus- or prefrontal cortex-dependent; therefore, it is perhaps better to take a circuit-level approach (69). The hippocampus projects to the infralimbic/prelimbic areas of the mPFC via a unidirectional glutamatergic pathway from the ventral two thirds of the CA1 and subiculum (115, 228, 297, 299, 598, 629). The CA1 and subiculum do not receive direct return projections from the mPFC in the rat (215). The prefrontal cortex is also indirectly connected to the dorsal hippocampus via the thalamus (607). Long-term potentiation can be induced in the mPFC by electrical stimulation of the CA1 (297-299). Direct electrode recordings from the CA1 and mPFC of the rat hippocampus indicate that correlated firing occurs in the two structures during spatial working memory, and this coordination may occur through entraining by hippocampal theta rhythms (311, 463). Furthermore, lesioning the mPFC reduces place field stability in the CA1 subregion of the hippocampus (325, 354, 535). Thus, the functional connections between the hippocampus and prefrontal cortex suggest a complex interplay between these regions. A detailed description of these interconnectivites is may be found in Vertes' (628) excellent review on subject.

Bilateral inactivation of the prelimbic area in rats does not impair performance in the working memory version of the 8 arm radial arm maze (173, 560). However, bilateral prelimbic

activation does impair working memory when a 30 minute delay is introduced between the 4th and 5th arm choices ("spatial win-shift"; (173, 212, 560). The projection from the ventral CA1/subiculum to the prelimbic area of the rodent mPFC is implicated in the ability to use trial-unique short-term memory to subsequently guide spatial search behavior (145). Floresco et al. (145) used bilateral lidocaine infusions to reversibly disconnect the ventral subiculum from contralateral prelimbic areas. This disconnection produced a disruption of spatial search specifically when success depended on retaining trial-specific information over a 30 minute delay. Together, these findings implicate the ventral CA1/subiculum to PL projection in control of information required to prospectively organize ongoing spatial behavior. Similarly, reversible disconnection lesions have demonstrated that mPFC-hippocampal communication is necessary for short-term memory in the water maze (644) and the T maze (645). Thus, while spatial navigation has long been recognized as hippocampus-dependent (e.g., (321), the prefrontal cortex also plays a role in aspects of spatial navigation, particularly when short-term memory is required.

While no task can be said to be 'purely' hippocampal or prefrontal, there are tasks in which the prefrontal cortex is preferentially activated with little hippocampal involvement. For example, performance in the non-spatial delayed alternation T-maze task is mediated by the integrity of the prefrontal cortex but not hippocampus (224). In this task, subjects must use intramaze cues to encode the previous location of a reward and retain this information over a delay to subsequently choose a new arm. When intramaze cues are eliminated and replaced by extramaze (and hence spatial) cues, this task becomes hippocampus-dependent (5). There are multiple parallel neural systems involved in spatial memory, including the hippocampus, dorsal striatum, amygdala (417) and prefrontal cortex. No one task recruits a single area exclusively. Instead, these circuitries work in parallel (417), in coordination, and/or in competition (368) depending on task parameters. Thus, subtle task variations can cause various brain regions to be differentially recruited. Consequently, the literature concerning the effects of sex or sex hormones on cognition must be interpreted with careful attention to the type of task utilized (as discussed below).

The contributions of the prefrontal cortex and hippocampus can be partially dissociated in spatial memory tasks by manipulating task demands. Spatial memory tasks are hippocampus-dependent (321), but also recruit the prefrontal cortex when trial-specific information is required to guide prospective behavior. Thus, the reference version of the Morris Water Maze, in which a rat must use spatial cues to navigate to the unchanging location of a hidden platform, is hippocampus-dependent (321, 444). When instead the location of the hidden platform is changed every training session, introducing working memory demands, the prefrontal cortex and hippocampus are jointly recruited (311, 369, 643). The standard version of the radial arm maze, in which all arms of the maze are baited, assesses working memory. Working and reference memory errors can also be tested separately in the radial arm maze in a paradigm in which animals use extra-maze cues to navigate to a subset of arms that is baited on every trial. In this model, an animal is considered to have committed a working memory error when it re-enters a baited arm, a reference memory error when it enters an arm that is never baited, and working/reference memory error when it re-enters an arm that is never baited. These measures can provide clues regarding a failure in a working memory system versus a reference memory system, but the roles of the hippocampus and prefrontal cortex cannot be fully dissociated without conducting lesion or inactivation studies.

In humans, too, dissociating prefrontal and hippocampal contributions to performance deficits is difficult. Interestingly, patients with frontal lesions and amygdala/hippocampal excisions demonstrate different deficits on a task of spatial working memory that requires memory for object-location associations (471). Patients with frontal lobe excisions fail when searching through a computerized array of boxes for rewards due to inefficient search strategy use. In contrast, patients with hippocampectomies were impaired only at more difficult task levels, likely because they were able to compensate for mnemonic deficits using efficient search strategy (471). These results suggesting that the unique contributions of the hippocampus and prefrontal cortex may be dissociable to an extent in specific tasks. Similarly, impairment in a verbal fluency task could arise as a result of a mnemonic/hippocampal deficiency or due to inefficient retrieval/'clustering' strategy (377). Examining the pattern of results, such as number and size of clusters, can help

provide an indication of the relative contribution of the prefrontal cortex to an observed deficit during neuropsychological testing (377).

Estrogens and Androgens

Estrogens

17β estradiol is the most potent of the estrogens. In females it is the primary circulating hormone produced before menopause (514) and is also the most widely studied of the estrogens. It binds to both ERα and ERβ receptors with greater affinity than estrone or estriol (485). Estradiol varies dramatically over the menstrual cycle and with age and intriguingly the variance across the course of the menstrual cycle is greater in 30-45 year old women than earlier in her reproductive period (332). Estradiol declines dramatically across menopause to about 10% of pre-menopausal levels (514). In contrast, estrone is present in lower concentrations than estradiol in young adulthood, declines more modestly across menopause and is subsequently found at higher levels than estradiol post-menopausally (514). 17-β estradiol and estrone can be interconverted enzymatically, but the preferential pathway is from estradiol to estrone (426). Estriol is heightened during pregnancy, and although there are a number of cognitive changes across gestation in the pregnant mother (395, 679) estriol will not be discussed further. 17α estradiol is an optical isomer of 17β estradiol and originates primarily from the adrenal glands (612) but will not be discussed. Additionally, local estrogen synthesis can occur in the hippocampus and perhaps other regions, and the relative contribution of locally synthesized estradiol on hippocampal and prefrontal cognition and function is a matter of considerable recent interest (See section, 'Local synthesis of estradiol').

Models for Studying Effects of Estrogens on Cognition

Endogenous Fluctuations in Estrogens

The menstrual cycle in women is associated with variations in ovarian hormones over a 28-32 day period (567), whereas in rodents, the estrous cycle is over 4 to 5 days (404). 17-β estradiol levels increase slowly over the diestrous phase, rapidly peak and fall on the day of proestrus, and reach a nadir during the estrous phase. Performance on various cognitive tasks fluctuate in correlation with phases of the menstrual cycle in women and the estrous cycle in rats (244, 331). For example, when endogenous estrogens are high, women perform relatively better on verbal fluency tasks and worse on spatial tasks (244). Note, however, that estradiol is not the only hormone to change endogenously with the menstrual/estrous cycle. Estrone levels range from 27.57 to 108.96 pg/ml across the rat estrous cycle (42), whereas estradiol levels range from as low as 10 pg/ml in diestrus to peak proestrus levels of 80 to 140 pg/ml (90, 456). However it is important to keep in mind that other hormones, such as progesterone, testosterone and luteinizing hormone levels fluctuate with the menstrual and estrous cycle as well as estrogens.

Deprivation of endogenous ovarian hormones is often studied experimentally in non-human models via ovariectomy. The bilateral removal of ovaries minimizes circulating gonadal hormones 24 hours after surgery (676). In women, natural menopause occurs over a period of ten years during which ovarian hormone secretion declines and ovulatory cycles become erratic and eventually cease (240). In rats, natural menopause can be modeled by administering 4-vinylcyclohexen diepoxide (VCD), which causes depletion of ovarian follicles similar to the process that occurs in naturally menopausal women (2, 3). The VCD model is relatively new, and takes weeks to manifest in reduced ovarian hormones rather than ovariectomy which usually takes only a few days to manifest as reduced circulating ovarian hormones. Given the lengthy time of manifestation and the relatively newer technique there are fewer studies using VCD. The cognitive effects of estrogens are also studied using exogenous administration of estrogens after ovariectomy in rodents. The cognitive and neuroplastic effects of exogenous hormone administration likely depend on the method of delivery, delivery schedule (tonic versus cyclic), in addition to dose and composition of estrogens, addition of progestins, timing of administration

after ovariectomy, age at administration, and task assessed. This literature will be reviewed in following sections.

Estrogen Receptors

Estradiol signaling is multifaceted and accomplished through several different means that include intracellular (nuclear, cytoplasmic) and membrane bound receptors. There are at least two intracellular estrogen receptors (ER), ER-α and ER-β and a membrane G-protein coupled receptor GPER. These ERs are distributed throughout the nervous system (156, 352) with ERα and ERβ are expressed differentially in regions throughout the neocortex (573). The hippocampus contains ER-α, ER-β and GPER receptors, whereas the prefrontal cortex contains mostly ERβ receptors (572, 573). In the hippocampus, intracellular ERs are located in the CA1, CA3, and the dentate gyrus in males and females although GPER staining appears scant through the CA3 region in females (144, 387, 399, 652); see Figure 4). Light and electron microscopy studies reveal ER α and β are located at extranuclear sites in neurons and glia of the hippocampus (436). ER receptor distribution in the hippocampus and prefrontal cortex are similar between adult males and females (347, 572, 573, 677). Intriguingly, despite similar distribution of ERs in the hippocampus and prefrontal cortex between males and females, there are sex differences in brain estradiol concentration in these regions depending on gonadectomy (51) reviewed below ('Local synthesis of estradiol').

ERs belong to the steroid receptor superfamily and function as ligand activated transcription factors (157, 614). As with most steroid receptors, ERs have a modular structure and contain a hormone binding domain, an activation of transcription domain, and a DNA binding domain that is important for interacting with the chromatin at unique Estrogen Response Elements (ERE) upstream of target genes (333, 353). In humans, the gene encoding ERα is located on chromosome 6, whereas the ERβ gene is located on chromosome 14 (157). Interestingly, there is low sequence homology between these isoforms (less than 50%), which is particularly evident in the ligand binding domain (156). ER signaling is very complex, which may owe to the fact that there are several different mRNA transcripts that arise from alternative splicing and promoter usage; the functional implications of these variants have yet to be fully determined (176).

A non-nuclear estrogen receptor, GPER, located in the endoplasmic reticulum also binds estradiol (525). GPER is expressed in several tissues throughout the periphery and brain (79), and activation of the receptor results in mobilization of intracellular calcium stores and activation of intracellular signaling molecules, such as adenylyl cyclase (525, 608). However more recently there has been some controversy over the exclusivity of GPER as an ER (364), as aldosterone activates GPER in muscle and epithelial cells (52, 229, 230). Thus, it appears estradiol signaling through ERs is very complicated, relying upon different isoforms residing intracellularly or at the level of the membrane. Specificity of estradiol action upon different regions of the brain is achieved by binding to specific cell types expressing the different ER isoforms; there are, however, several regions in which there is overlap in expression of these receptors (435).

Estrogen Receptor Signaling

The accepted model of estrogen receptor activation is similar to that of the AR (see Figure 5). Estrogens bind to ERs in the nucleus, a conformational change takes place resulting in recruitment of coactivator proteins and dimerization with other liganded ERs (72). The complex then moves into the nucleus to bind with EREs (5'-GGTCAnnnTGACC-3') to regulate estrogen responsive genes (334). ERs, though, can regulate genetic transcription of target genes, independent of direct interaction with an ERE, via regulation of other transcription factors that bind to cognate response elements that differ from ERE's (234). This transcriptional cross talk (234) functions via direct protein-protein interactions between an activated ER and a transcription factor, such as AP-1 (72), to regulate a multitude of genes that do not contain an ERE (for example, see (620). ERs reportedly also have rapid, non-genomic effects that happen too swiftly to induce protein production (see description above for GPER). For example, estradiol is known to stimulate the release of intracellular calcium and to activate the mitogen activated protein kinase (MAPK) cascade (394). Thus, while estradiol may ultimately lead to activation of a response element via initiation of second messenger systems, estrogen mediated non-genomic

effects happen too quickly for the stimulation of protein production and instead utilize the extant intracellular protein machinery. It has been suggested that the classic genomic and non-ERE necessary effects of estradiol are mediated by the intracellular ERs (α and β), with the non-genomic effects regulated via the membrane bound GPER (72). This complex action of signaling allows for a large range of genes to be regulated by estradiol, and an understanding of the molecular events may allow for the development of drugs that target individual components of the signaling process.

Estrogens and Hippocampal Physiology in Females

Estradiol modulates adult neurogenesis in the dentate gyrus (43, 191, 195, 469, 603), which in turn is associated with alterations in hippocampus-dependent cognition (196). In addition, the density of apical dendritic spines in CA1 hippocampal pyramidal cells varies as a function of the estrous cycle in rats and peaks during proestrus (220, 673, 674). Both dendritic spine number and synaptic density in the CA1 region of the female hippocampus are increased when endogenous estradiol levels are high akin to proestrous levels (671, 674). Intriguingly, hippocampus volume changes by approximately 2-3% over the course of the estrous cycle in mice, as measured by high-resolution MRI, possibly due in part to these alterations in synaptic density (508). Correspondingly, ovariectomy reduces apical spine densities in the CA1 region of the hippocampus compared to intact rats and high estradiol-treated rats (220, 641). Estradiol-associated fluctuations in spine densities are NMDA receptor dependent, as NMDA receptor antagonism, but not AMPA or muscarinic receptor antagonism, blocks the effects of estradiol on CA1 dendritic spine density (675). Further, estradiol increases sensitivity of these synapses to NMDA receptor-, but not AMPA receptor-, mediated input (677). Estradiol increases hippocampal synaptophysin expression in the CA1 region of the hippocampus (80, 397, 503) and dose-dependently increases synaptophysin in the CA3 region in female rodents (42). Estradiol's ability to modulate synaptic proteins is not limited to rodents; in female primates, medium-to-high levels of chronic estradiol administered in the mid-to-late follicular phase increase synaptophysin (presynaptic marker), and spinophilin (postsynaptic) levels in the CA1 (109, 249).

In female rats, proestrus is also associated with enhanced long-term potentiation in the CA1 response to Schaffer collateral stimulation (550, 648). This may be mediated by altered binding of glutamate and GABA in the CA1 with fluctuations in estradiol (556, 653). The threshold for electrically induced seizures of the dorsal hippocampus is also lowest during proestrus (606). Women with epilepsy have a lower seizure threshold when in the midluteal phase of their menstrual cycle (91). Together, these findings suggest that the excitability of the hippocampus is increased with increased endogenous levels of estradiol in both the rodent and primates, and this is correlated with changes in synapse density, synaptic proteins and long term potentiation.

Functional MRI studies also find different patterns of activity and/or perfusion during hippocampus-dependent cognitive tasks across the menstrual cycle. Alterations in activity include but are not limited to the hippocampus. Schöning et al. (2007) found differences across the menstrual cycle in brain activation patterns while performing a mental rotation task. In particular, the left and right middle temporal gyrus, the left lentiform nucleus and thalamus, the left and right cingulated gyrus, the corpus callosum, the superior occipital and angular gyrus, and the right middle and superior frontal gyrus had increased activation during the midluteal stage (high endogenous estradiol) compared to the early follicular phase (low estradiol). Dietrich (2001) found that blood oxygenation level-dependent (BOLD) signals increased on days 11/12 of the menstrual cycle compared to menses during verbal, spatial, and motor tasks, without any change in the pattern of cortical activation. In rats, brain activation can be studied using immediate early genes (IEG)s such as c-fos or zif268. Limited studies exist examining the effects of immediate early gene activation differences with estradiol level in the hippocampus but those few that do exist do not show differences in IEG expression with estradiol level in the dentate gyrus (415). There are a couple of studies examining sex differences in IEG expression in response to spatial memory retrieval and/or pattern separation. These studies find that females have greater IEG expression in new neurons in the dentate gyrus in response to spatial memory retrieval (110) and in response to pattern separation (685). In terms of pattern separation, there were sex differences in the type of IEG activated in the CA3 region of the hippocampus and in the association of IEG

expression and performance with idiothetic and spatial strategy user (685). Thus, sex differences and endogenous increases in estradiol are associated with increased activity levels in a number of brain regions, including but not limited to the hippocampus and prefrontal cortex.

Estrogens and hippocampus-dependent cognition

Estrogens modulate hippocampus-dependent learning and memory in female rodents (44), non-human primates (355) and women (244). Although there is not consensus on the matter (e.g.,(505),data suggest that hippocampus-dependent cognition has an inverted U-shaped relationship to estradiol levels in females (145).

As previously discussed, one method of studying contributions of estrogens to cognition is to observe changes in cognition across the estrous or menstrual cycle. In women, the low physiological level of ovarian hormones during menses are associated with improved performance on spatial rotation tasks compared to women during the midluteal phase or the preovulatory surge (244, 257, 402, 441, 495, 558). Among young women with regular menstrual cycles or taking oral contraceptives, estradiol levels correlate negatively with mental rotation ability (118, 257, 335, 402). Interestingly, men have better performance in the Mental Rotation Test compared to women who are in the midluteal phase of the menstrual cycle, but not compared to women in the follicular phase or menses (135, 558). However, a recent meta-analysis found that mental rotation accuracy is not improved in the early follicular phase (500), when estradiol levels are low. The differences in findings may be due to studies that rely on young adult women compared to older women; as noted earlier women in their 30s show greater fluctuations in estradiol levels across the menstrual cycle than women in their early 20s (332). In young cycling primates, spatial memory as assessed using a Delayed Recognition Span Test is significantly better during the follicular and luteal (low estradiol) phases of the menstrual cycle than during the peri-ovulatory (high) phase of the cycle (359). In rodents, too, the high endogenous estradiol levels present during proestrus or during the breeding season are associated with impairments in spatial navigation (184, 190, 193, 649). For example, males outperform proestrous females in initial trials of a standard Morris water maze, whereas diestrous females perform similarly to males (184). Further, proestrous females have impaired spatial contextual conditioning (hippocampus-dependent) than males or estrous females while showing similar cue (hippocampus-independent) conditioning (408). In women, estradiol levels are implicated in consolidation of memory and/or maintenance of extinction. Women have greater extinction memory, indicating less recovery of fear memory, when estradiol levels are high (222, 425, 689). Thus, across a number of species, evidence from naturally cycling females suggests an inverted-U shaped relation between hippocampal function and endogenous estradiol levels. Nevertheless, as previously mentioned, there is no consensus regarding the influence of the estrous cycle on learning and memory. There have been several negative findings regarding the effects of the menstrual/estrous cycle on hippocampus-dependent learning in humans (e.g., (500) and rodents respectively (60, 595) but it is important to note that estradiol levels vary dramatically across days and age in women. In rodents, estradiol and progesterone level vary dramatically on time of day and thus within hours. Thus some studies may miss the peak of estradiol concentration or have tested younger rather than older cycling women that may account for variability in study outcome (330). A recent meta-analysis indicates that there are no sex differences in variability on a number of behavioral, molecular and physiological measures (505). This has been interpreted as evidence that estrous cycle monitoring is not necessary; however an absence of sex differences in variability does not preclude the idea that variability in females is influenced by estrous cycle. Given the estrous cycle differences on multiple measures of hippocampus function, electrophysiology and structure (106, 341, 649, 672) we urge the research community to continue to monitor estrous cycling phase when examining measures involving the hippocampus.

Studies investigating the effects of estradiol on cognition using exogenous replacement of estradiol after ovariectomy further support a relation between estradiol and hippocampal cognition. In rats, estradiol replacement at high levels after ovariectomy results in a female disadvantage in early acquisition, whereas estradiol replacement at medium levels results in similar performance to males (184). In contrast, at high physiological (proestrous levels) to supraphysiological (greater than proestrous) levels, estradiol negatively impacts reference

memory in the female rat (197). However in contrast, a supraphysiological dose of estradiol to ovariectomized rats did not significantly affect working memory performance in either the spatial radial arm maze, a task which performance relies on the hippocampus, or the spatial delayed win-shift task, in which performance relies on both the prefrontal cortex and the hippocampus (197). Further, high estradiol impairs, whereas low estradiol facilitates, contextual conditioning in adult ovariectomized rats (42). Acute estradiol injection may enhance spatial memory consolidation in a time- and dose-dependent manner; Packard and Teather (475) trained rats in the standard Morris Water Maze in a single 8-trial session. Intraperitoneal injection of estradiol-cyclodextrin (.2, but not .1 or .4 mg/kg) immediately but not 2 hours post-training improved escape latencies on a retention task 24 hours later. Together, these findings suggest estradiol levels that are too high or too low result in impaired performance on tasks that require the hippocampus, and support the notion that there is an optimal level of estradiol in regulating performance on these tasks. For reviews on the relation between estradiol and hippocampal cognition please see 44, 145, 392,179, 181, 618).

Spatial Strategy

Endogenous fluctuations in ovarian hormones also alter females' spatial strategy selection (340, 341, 498, 537). Rats that are tested in proestrus, when endogenous estradiol is high, show preference for a hippocampus-dependent place strategy significantly more often than a hippocampus-independent response strategy compared to rats in estrus, who show the reverse pattern (340, 537). Estradiol-dependent shifts in learning strategy in gonadally intact female rats have been attributed to disinhibition of the hippocampus with high estradiol (418). Considering the previously-discussed association between high endogenous estradiol levels and impaired performance in hippocampus-dependent tasks, high estradiol levels may be associated with increased reliance on compromised hippocampal strategies. Ovariectomy is associated with a bias towards using a response-based strategy during spatial navigation in young female rats (341). However, ovariectomized rats given medium to supraphysiological levels of estradiol adopt allocentric strategies (126, 128, 341). Changes in hippocampal volume across the estrous cycle in mice, are associated with switching between hippocampal and striatal strategies in the T maze within these same mice (508). Estrus is associated with decreased hippocampal volume and use of a response strategy, whereas proestrus is associated with increased hippocampal volume and use of a place strategy (508, 537). In women parahippocampal gyrus volume changes in size over the course of the menstrual cycle, with larger volumes in the right parahippocampal gyrus during early follicular (low estradiol) compared to the mid-luteal phase (498). Thus, spatial strategy selection covaries with alterations in hippocampal volume in both humans and rodents.

Estrogens and Prefrontal Cortex–dependent Cognition

There is thought to be an inverted U-shaped curvilinear function that describes the relationship between estrogens and prefrontal cortex-dependent cognition, as there is for estrogens and hippocampal function (565), see above). Young women perform better on the Wisconsin Card Sorting Task (WCST), which measures aspects of prefrontal cortical function, in the menses phase, and perform worse during the ovulatory phase of the menstrual cycle (588). Increases in endogenous estradiol levels during the menstrual cycle are associated with increases in verbal working memory (244, 533). Estradiol levels correlate positively with verbal fluency among women with regular menstrual cycles or taking oral contraceptives (335, 402). Oral contraception use, which decreases salivary 17β-estradiol and progesterone levels, is associated with poorer performance on verbal fluency tasks compared to natural cycling women (226).

In rodents, a number of studies have investigated estradiol's effects on prefrontal cortical function in tasks that are relatively independent of hippocampal involvement. Low physiological levels of estradiol facilitate whereas high physiological levels of estradiol impair performance on a non-spatial delayed alternation T-maze (659), a task mediated by the prefrontal cortex and not the hippocampus. There is a delay-dependent effect, such that high levels of estradiol impair prefrontal cortex-dependent working memory at longer delays and low levels weakly facilitate prefrontal cortex-dependent working memory at a shorter delay (659). Proestrous levels of

estradiol impair performance in the differential reinforcement of low rates of responding (DRL) task, which assesses prefrontal cortex-mediated response inhibition (647). Ovariectomy reduces performance in the spontaneous alternation T-maze (428), another task that relies on the prefrontal cortex (361), and these impairments are reversed by 10-day treatment with low physiological levels of 17β estradiol in young mice (428). Similarly, three weeks of daily low physiological levels of estradiol (5 µg/kg, subcutaneous) significantly increases performance during spontaneous alternation T-maze acquisition compared to ovariectomized controls (164).These data suggest that estradiol's effects on prefrontal cortex-dependent working memory may be different depending on task demands, including demands on prospective memory. Ovariectomy and estradiol also modulate effort-based decision-making in female rats (619). That is, ovariectomy increases choice of a high-reward/high effort lever, whereas replacement with high but not low physiological levels of estradiol benzoate shifts responding toward a low-reward/ low-effort lever (619). Effort-based decision making depends on the integrity of dopaminergic transmission in the prefrontal cortex, nucleus accumbens, and amygdala (172, 174). Together, these findings indicate that prefrontal cortex-mediated behaviors that do not depend on the hippocampus are also modulated by estradiol.

As is the case for the hippocampus, fluctuations in estrogens are associated with altered volume and activity of the prefrontal cortex. Women using hormonal contraceptives have significantly larger prefrontal cortices, pre- and postcentral gyri, parahippocampal and fusiform gyri and temporal regions, compared to women not using contraceptives (498). Resting state functional connectivity between the left angular gyrus, middle frontal gyrus, and anterior cingulated cortex are modulated by menstrual cycle phase and oral contraceptive use (492). In particular, oral contraceptive use and the luteal phase are associated with reduced connectivity between these regions, which are associated with cognitive and affective control (492). Further, interhemispheric correlation between frontal regions is higher during ovulation and lower in the menses phase, whereas the opposite pattern in intrahemispheric connectivity is seen in occipital regions (588). As previously noted, in both the follicular and midluteal cycle phases, females' frontal and parietal brain activation in response to a mental rotation task is significantly correlated with serum estradiol levels (558). Additionally, brain activation in the left inferior frontal gyrus, which is implicated in verbal memory retrieval, is correlated positively with plasma estradiol concentration during a verbal encoding task (119). Together, these studies indicates that estradiol levels can alter activation in the prefrontal cortex in women.

Estradiol and Spatial Working Memory

As reviewed above, the integrity of both the prefrontal cortex and hippocampus is important for optimal performance in spatial working memory tasks. Compared to intact, cycling rodents, young adult ovariectomized rodents have impaired working memory performance on the radial arm maze (64, 127, 662). Low and moderate physiological levels of estradiol improve spatial working memory in young adult females (64, 124, 165, 205, 281, 393). In contrast, high to supraphysiological levels of estradiol fail to improve spatial working memory in ovariectomized rats (197, 391).

Estradiol dose-dependently alters spatial working memory depending on task demands. Bimonte and Denenberg (64) found that estradiol facilitates a water-escape version of radial arm maze performance particularly after several arm choices, when the amount of trial- specific information ("working memory load") is presumably greater. In this study, low levels of estradiol were sufficient to improve performance only early in the trial (low working memory demands), whereas moderate estradiol levels were required to improve performance later in the trial (higher working memory demands). Thus, estradiol may dose-dependently affect spatial working memory performance as working memory load or prospective memory load increases.

Working and reference memory may be differentially altered within spatial navigation tasks by different doses of estradiol. Holmes et al. (281) found that low levels of estradiol specifically facilitated working memory without affecting reference memory in the working/reference memory version of the radial arm maze. Similarly, Fader et al. (165) found that diestrous-level estradiol facilitated working memory and not reference memory during acquisition in the radial arm maze. However, high physiological doses of estradiol impaired working memory compared to ovariectomized controls in the working/reference memory version of the radial arm

maze (281). Together, these findings suggest that estradiol may dose-dependently affect working versus reference memory performance, with facilitation of working memory by low physiological doses of estradiol and impairments of working memory and reference memory at high physiological levels of estradiol (see above).

Infusions into the dorsal hippocampus or prefrontal cortex facilitate working memory in a delayed win-shift version of the radial arm maze, but at different doses. Specifically, a higher dose of estradiol cyclodextrin (0.9µg) facilitates working memory when infused into the prefrontal cortex, whereas a lower dose (.1 µg) of estradiol facilitates performance when infused into the dorsal hippocampus (580). Additionally, working memory is significantly impaired 24 h after infusions of estradiol into the dorsal hippocampus but not the prefrontal cortex (580). Effects on performance at these timescales suggest genomic signaling in the dorsal hippocampus, and non-genomic signaling in the prefrontal cortex (580). Thus, although similar inverted U-shaped curvilinear functions between estradiol and hippocampal and prefrontal cortex function have been proposed, estradiol might alter the function of the prefrontal cortex-hippocampal circuit in task-, time- and dose- specific ways.

Estrone

The great majority of studies on estrogens and cognition have been conducted with estradiol. However, studies have begun to look at the effects of estrone and estrone-based hormone therapies on hippocampal and prefrontal cortex structure and function in females. Estrone decreases the survival of new neurons in the hippocampus following performance in a spatial memory task in adult female rats, whereas 17β estradiol increases the survival of new neurons (415). Estrone dose-dependently impairs contextual fear conditioning, a form of hippocampus-dependent learning and memory, while as mentioned earlier estradiol dose-dependently facilitates or impaired contextual fear conditioning when administered acutely to ovariectomized adult female rats (42). Specifically, whereas low physiological doses of 17β-estradiol increased and high pharmacological doses of estradiol decreased contextual fear conditioning, estrone only impaired freezing behavior, at a moderate-to-high physiological dose. In contrast to these findings, Engler-Chiurrazzi et al. (155) found that in the delayed-match-to-sample water maze, a chronic regimen of a high estrone dose (8.0 µg/day) impaired memory performance during acquisition (increasing number of errors) and after a 6 and 8 hour delay challenge. Further, chronic estrone treatment did not alter spatial reference acquisition or memory in the Morris Water Maze (155, 415). Together, these findings indicate that hippocampal plasticity and function are modulated differently by estrone and estradiol.

As mentioned earlier, Premarin is the most commonly prescribed hormone therapy in postmenopausal women in the United States, although hormone therapy usage has declined in recent decades (269). Premarin is a conjugated equine estrogen (CEE) containing a mixture of at least 10 compounds including equilin (15-25%) and trace amounts (0.5%) of sulfated 17β estradiol, but comprised mainly (50%) of sulfated estrone (63). At doses equivalent to those prescribed to women, Premarin and Progynova (estradiol valerate) differentially regulate ER expression in the hippocampus and cortex (306). Whereas Progynova up-regulates ERβ expression in the hippocampus and cortex, Premarin downregulates ERα expression in the hippocampus and cortex (306).

Several animal studies have begun to describe the relation between Premarin and hippocampal and prefrontal cognition. Engler-Chiurrazzi et al. (2011) gave tonic Premarin at levels analogous low, medium, or high (approximately ½, 1 or 1.5 the levels the usual daily dose given to women, scaled to rodent body mass(154). Low-dose tonic Premarin treatment impaired learning the Morris Water Maze (spatial reference memory) and the delayed-match-to-sample plus maze (spatial working memory), but had no significant effect in the working/reference memory version of a water radial arm maze (154). Partly consistent with these findings, low-dose daily Premarin impaired spatial reference and working memory compared to ovariectomized controls in the working/reference memory version of the radial arm maze (45). High doses of tonic Premarin reduced the number of errors in a delayed matching to sample plus maze when a 6 hour delay was introduced between trials 2 and 3 (154). Medium and high tonic Premarin doses also improved performance in the reference Morris Water Maze task (155). These results suggest that low doses of Premarin may impair spatial reference and working memory, and high doses of

Premarin facilitate spatial and working memory. However, others (2) have found that cyclic low, medium, or high dose of Premarin all similarly enhance various aspects of spatial learning and memory, including delayed match to sample performance and reduced overnight forgetting during reference water maze training. Variations in study outcomes may be influenced by administration schedule (e.g., cyclic versus tonic administration) or task choice, and further studies are warranted to better understand the effects of estrone and Premarin on hippocampal and prefrontal cortical function. As noted earlier, while estrone and estradiol are interconverted by oxidoreductase 17β-hydroxysteroid dehydrogenase (329), the preferential pathway is estradiol to estrone. Additionally, estrone-based therapies and estrone administration increase 17β-estradiol levels but not to same degree (e.g., (2). Further, the multiple components of Premarin may act together or independently to alter cognition differently than estrone alone, and the contribution of other components is now being investigated by some groups (e.g., (600).

Local synthesis of estradiol

It is evident that ovariectomy can profoundly influence aspects of hippocampal and prefrontal cognition, spine density in the CA1 region, and neurogenesis via cell proliferation in the dentate gyrus (see previous sections). However, it is important to note that the mRNA for the enzymes necessary to synthesize estrogens and androgens are present in the adult male and female rat hippocampus (277, 317), and much has been made in recent years of the possibility that estradiol may be synthesized locally in the brain via aromatase, or even de novo. Many studies point to the comparison of steroid hormone concentrations being higher in the brain compared to serum as support for de novo synthesis. However it should be noted that steroid hormones are both lipophilic and hydrophic, and they require carrier proteins (such as sex hormone binding globulin) to be transported in aqueous solutions such as plasma. Thus steroid hormones may be sequestered in lipid-filled tissue such as the brain, and it therefore is not be so surprising if lipid-dense tissue with a higher concentration of steroid receptors, such as brain, has higher levels of steroid hormones than aqueous matter such as serum or plasma. In addition, much of the data supporting de novo synthesis has been obtained from neonatal brains, avian species and the Wistar rat. Wistar rats, as outlined in the section below ('Androgens: AR distribution in the Hippocampus and PFC'), are exhibit significant AR expression in the dentate gyrus, compared to other strains and may have altered sequestering of androgens and estrogens in the dentate compared to other rat strains. However, overall the findings point to perhaps a greater role of neurosteroid production of estradiol in neonatal rodents and in avian species and in adult male, but not female rodents.

There are few studies of hormones in brain in adult male rats and even fewer in adult female rats. Kato et al. (2013) found that the concentration of 17β-estradiol is approximately 3-4 times greater in the hippocampus of a female Wistar rat in proestrus compared female rats in other stages of the cycle, matching the relative concentration of plasma levels of estradiol across the estrous cycle (317). Intriguingly adult male Wistar rats have significantly higher estradiol levels in the hippocampus (278) than levels reported in the female hippocampus during proestrus (317). Importantly, significant levels of estradiol have been detected in the hippocampus of adult male Wistar rats one week but not three weeks (in Sprague Dawley rats) after castration (278, 317). This suggests that the hippocampus synthesizes estradiol in the absence of testes at least in Wistar but not Sprague-Dawley, rats. However levels of estradiol were reduced by 20% (278) in castrated compared to intact adult male Wistar rats. Importantly, two- three weeks after ovariectomy in female Wistar and Sprague-Dawley rats, hippocampal estradiol levels were reduced by 84-90% compared to proestrous levels (50, 168, 311). However at least in Wistar rats, 2 weeks after ovariectomy estradiol levels in the hippocampus were not significantly different from levels seen in non-proestrous females (317), Together, these findings indicate that hippocampal levels of estradiol may be robust against castration in adult male Wistar rats but that levels decrease dramatically with ovariectomy in both adult female Wistar and Sprague Dawley rats. This indicates that while there may be evidence of local synthesis of estradiol in adult male Wistar rats there is little evidence to support local synthesis in adult female rats.

In vitro studies using neonatal and sometimes adult brain tissue have provided some support for the local synthesis or de novo synthesis of estradiol. Generally, these studies use aromatase inhibitors to block conversion of testosterone into estradiol (but note this also will block

conversion of androstenedione to estrone (e.g., (623). Aromatase inhibition within the hippocampus significantly decreases hippocampal 17β-estradiol levels, synaptic proteins, and dendritic spine density in vitro from cultures derived from neonatal brains (345, 504). This suggests that hippocampus-derived estradiol is important in maintenance of hippocampal synapses in ontogeny (317). In vitro studies using cultures derived from adult male and female rat brains, aromatase inhibition decreases hippocampal synapse density and hippocampal 17β-estradiol levels similarly in males and females (168, 538). In vivo, however, systemic application of Letrozole (aromatase inhibitor) induces synapse loss in adult female but not male rats (168). However, in this same study estradiol levels were undetectable in ovariectomized females compared to higher levels in intact proestrous rats (168). In addition, in another study (690) letrozole had a much reduced effect to reduce spine density in the hippocampus of ovariectomized female mice (~8% drop) compared to a greater effect in intact mice (~ 40% drop). Regarding cognition, systemic blockade of aromatase using Fadrozole impairs fear extinction in intact adult male rats (223) and hippocampal infusions impaired spatial memory in male zebra finches (34). Systemic blockade of aromatase by Letrozole impaired Schaeffer-collateral long-term potentiation (LTP) in gonadally intact male and female rats and ovariectomized rats (630). However, while the deficits in LTP were greater in females compared to males, the authors did not control for estrous cycle (630) which is known to affect LTP (648). Thus while systemic aromatase blockade induces synapse loss and LTP to a greater extent in adult female than male rats (168), these findings are limited to intact females suggesting that de novo synthesis of estradiol in females may be limited.

In humans, aromatase has been detected in the basal forebrain, cerebral cortex, hippocampus, thalamus, cerebellum and brainstem through post-mortem immunocytochemistry and other techniques (31). Possibly consistent with these pre-clinical findings in non-human animals, cognitive deficits have been reported in women taking aromatase-inhibitors as part of treatment for hormone-dependent breast cancer (see (496) for a review of this literature). Together, these findings suggest that conversion of testosterone to estradiol by aromatase could potentially contribute to cognition and synaptic plasticity across species, including in humans. However it should be noted that peripherally-synthesized non-gonadal steroid synthesis of estradiol may very well contribute to the concentrations observed in the brain even after gonadectomy. For example, small amounts of DHEA, androstenedione, androstendiol and estradiol, are produced in the adrenal cortex, and estradiol is also synthesized in adipose tissue (455, 579). Thus, the evidence for de novo synthesis from these studies are not strong as the majority of these studies have used systemic, not local, blockade of aromatase.

In summary, while much has been made of the possibility that local or de novo synthesis contribute to estradiol concentrations in the brain, much of the direct data supporting local and de novo synthesis comes from neonatal brain tissue, avian species, and in the adult male Wistar rat strain. Future studies need to determine whether or not sex differences exist in the ability of local synthesis of estradiol in the adult brain without intact gonads. Indeed this may not be a surprising outcome given that many of the effects of testosterone in males are via estradiol (and hence a local conversion of testosterone to estradiol via aromatase is likely in the male brain). Given that there are well known significant impairments in cognition (and appetitive and consummatory sexual behavior) following gonadectomy in both the rodent and human, this suggests that local or de novo synthesis of estrogens may not contribute profoundly to long-term changes in cognition in the adult rodent or primate.

Progestins

It is important to note that both estradiol and progesterone fluctuate across the estrous cycle (90), and that loss of ovarian function reduces progesterone levels in addition to estradiol levels (68, 567). Thus, an understanding of the joint and separate effects of estradiol and progesterone on learning and memory and neural plasticity is needed. This is especially relevant in the context of hormone therapy, where progestins are administered concomitantly with estrogens in women with uteruses, as estrogen therapy alone is associated with increased risk for cancers but progesterone administration offsets this risk (584). Progesterone receptors (PR)

are located in a variety of brain regions, including the CA3 region of the hippocampus, and are expressed in two isoforms PR-A and PR-B (405). PR expression is induced by estradiol in adult female rodents in many regions of the brain including the amygdala, medial preoptic area, regions of the hypothalamus and the hippocampus (405).

Rodent studies have begun to disentangle some of the relative and combined effects of progesterone and estradiol on learning and memory in females. Naturally cycling female rats have better consolidation of fear extinction when trained during proestrus (high estrogen and progesterone) compared to metestrus (low estrogen/progesterone; (424). Blocking either estradiol or progesterone receptors prior to training in proestrus impaired extinction recall when rats were tested the next day, whereas exogenous administration of estradiol or progesterone during metestrus improved extinction recall (424). Post-training injections of progesterone in ovariectomized adult rats improves performance on the reference version of the Morris water maze, object recognition, Y maze task, and conditioned place preference compared to administration of a vehicle in young rats (186). In middle aged male and female mice (sexes not separately analyzed), progesterone on its own improved performance in object placement, water maze, contextual and cued fear conditioning tasks (187). Thus, in several studies, progesterone alone has been found to have positive effects on aspects of cognition in rats, while others (e.g., (106) have found null effects of progesterone alone on reference memory.

Chesler and Juraska (2000) found that neither pre-training injections of progesterone or estradiol alone (5 micrograms) influenced acquisition in the standard Morris water maze task in young female rats, but both hormones administered in combination impaired acquisition (106). Natural progesterone also abolishes 17β-estradiol-induced benefits in the reference version of the Morris water maze (65). Thus, estradiol and progesterone interact to influence cognition in female rodents. Neither component alone nor their combination alters performance in the non-spatial Morris water maze in young adult female rats, suggesting possible hippocampal specificity on the effects of progesterone (106). Interaction between progesterone and estradiol may be age-dependent, as chronic progesterone plus estradiol treatment facilitates performance in the standard Morris water maze in middle aged females (407). Less is known about effects of progesterone on prefrontal cortex-mediated behaviors. Long-term progesterone treatment plus 17β-estradiol or 17β-estradiol alone improves performance on the spatial delayed matching position T-maze compared to ovariectomy in aged rats (108, 206).

The same methodological variables that have been shown to influence the effects of estrogens on cognition – age, method of administration, dosage regimen (cyclic, tonic), dosage chronicity, and reproductive status of subjects - complicate comparison of results regarding progesterone administration. Some studies (e.g., (386) use retired breeders or oral administration of hormone, which is metabolized differently and poses challenges for dosage control. Further, natural versus synthetic progestins have different effects on cognition in rats depending on task type, with more negative outcomes associated with use of synthetic progestins such as medroxyprogesterone acetate (MPA) (e.g., (77, 78, 108, 386). For example, tonic MPA impairs memory retention after a delay on the water radial arm maze, and exacerbates overnight forgetting on the spatial reference memory Morris water maze (78). MPA in combination with 17β-estradiol treatment impairs spatial reference memory relative to 17β-estradiol treatment alone or progesterone plus 17β-estradiol treatment in aged ovariectomized rats (108). In spatial working memory tasks, MPA-associated impairments were greater with higher levels of working memory load both in young and older ovariectomized adult rats (77, 78). MPA administration may have long-term effects on spatial working memory beyond the time frame of administration, as MPA administered in either young adulthood, or middle-age, impaired water radial-arm maze and Morris water maze performance when measured in middle age (77), with more pronounced effects seen with MPA administration in both young and middle adulthood. The detrimental effects of MPA in combination with 17β-estradiol is task dependent, as chronic administration of MPA plus 17β-estradiol was beneficial on an alternation T-maze task, perhaps related to the fact that this task can be solved using either a spatial or a non-spatial strategy (108).

Progesterone on its own has neuroprotective properties in vitro (318, 458) and in vivo (97, 494), while MPA does not (458). Regarding the combined effects of progesterone with estradiol, several studies indicate that progesterone or MPA attenuates the neurotrophic effects of estradiol in vitro and in vivo (6, 7, 66, 96, 300, 532); but see (384, 458). Relative to

progesterone, MPA has been found to cause greater attenuation of 17β-estradiol-induced neurotrophic actions (458). As previously noted, in the hippocampus, estradiol enhances neural excitability (606) and dendritic spine density (451). Acute estradiol administration in ovariectomized rats also transiently increases cell proliferation in the dentate gyrus (49, 603). However, an acute injection of progesterone given after estradiol treatment reverses the estradiol-induced increase in cell proliferation in adult ovariectomized rats (602). Progesterone also antagonizes the effect of estradiol to increase CA1 spine density in vitro and in vivo in females (450, 563). EB+MPA treatment decreased neurogenesis in the dentate gyrus relative to oil treatment, whereas Progesterone + EB treatment did not significantly alter neurogenesis in female rats (99). These findings stand in contrast to studies in male mice that find that 7 days of daily treatment with progesterone can increase neurogenesis in the dentate gyrus via cell proliferation but not short-term cell survival (47). This finding serves as an illustration that progesterone and estradiol may act differently in males and females (explored further in a subsequent section).

Together, the animal literature indicates that the type of progestin (natural progesterone versus synthetic MPA) affects both short- and long-term effects of hormone administration. Thus, although it is evident that progestins modulate hippocampal and prefrontal cortex-mediated cognition, the relative role of estradiol versus progesterone, across the estrous cycle, aging, or ovariectomy/menopause, warrants further study. This remains an important area for consideration, particularly considering that women are commonly prescribed progestins to offset cancer risk associated with estrogen HT (584). In women, progestins, particularly synthetic variants, may have a negative impact on hippocampal and prefrontal cognition alone or when combined with estrogens in HT. For example, the landmark WHIMS study found that postmenopausal women taking Premarin therapy (CEE) alone did not differ significantly in risk for dementia from women taking placebo (though mean differences were towards greater risk),whereas women taking CEE plus MPA were significantly more likely to be diagnosed with dementia compared to women receiving placebo treatment (574). It is also important to bear in mind that progesterone initially enhances estradiol-induced sexual receptivity in female rodents, but then serves to terminate receptivity and induce sexual refractoriness 24 hours later (453) . Mechanistically, this effect on sexual behavior is initiated by estradiol as systemic treatment increases the expression of progesterone receptors in regions associated with reproductive behavior such as the hypothalamus (398), amygdala, medial preoptic area (405) and spinal cord (439). As noted earlier PR expression is induced by estradiol even in the hippocampus, thus perhaps it should not be surprising that there may be biphasic effects of progesterone on cognition, depending on background estradiol levels (and PR expression) (405).

Estradiol and progestin effects in males

The majority of research concerning the effects of 17β-estradiol on hippocampal and prefrontal cortex morphology, plasticity, and memory has been done in females, thus broad conclusions about males are more difficult to draw. However, there is evidence that estrogens affect neural function and behavior in males. A single post-training local infusion of estradiol directly into the hippocampus enhances retention in the reference memory in the Morris water maze in gonadally intact adult male rats (474). In gonadally intact male mice, chronic estradiol administration improved both spatial reference and working memory in the radial arm maze and T-maze (261). Chronic treatment of gonadectomized male rats with estradiol but not testosterone, enhances spatial working memory in the radial arm maze, and improves learning in a delayed-match-to-position T-maze task (207, 209, 391). Estradiol also reverses gonadectomy-induced impairments in the Barnes Maze in adult male rats (381), a task in which performance is also improved by testosterone (381). However long-term tonic estradiol administration (via pellets) did not reverse the gonadectomy-induced deficits in spatial alternation or several non-spatial prefrontal-cortex-mediated behaviors, whereas testosterone did reverse the deficits (349). Thus, some types of spatial- and non-spatial memory are more susceptible to modulation by estradiol versus testosterone in males. Given that non-spatial memory tasks are sensitive to testosterone but not estradiol, it appears that testosterone may have more of an influence in the prefrontal

cortex of males whereas estradiol may preferentially influence the function of the hippocampus in males. Indeed, older males may be more sensitive to the effects of estradiol in working memory as, when a 1 hour delay is instituted between the 4th and 4th arm choices on a spatial radial arm maze, estradiol administration is associated with a small improvement in aged males but not in aged females (391). Together, these studies demonstrate that, as in females, estradiol influences cognitive performance in males. Estradiol modulation of cognition in males is task-specific and perhaps age-specific, and estradiol and testosterone appear to affect distinct cognitive domains in males. Because testosterone can be converted to estradiol (and other metabolites), isolating the role of androgens and estrogens in specific aspects of learning and memory is an important task. For example in men, inhibition of aromatase (blocking the conversion of testosterone to estradiol) prevents testosterone-induced improvement of verbal memory in older men (102). In contrast, testosterone-induced improvements in spatial memory are independent of conversion to estradiol (102). Rodent models are also illustrative of the principle that testosterone may alter aspects cognition in males partly through aromatization to estradiol (e.g., (151, 371).

Studies directly comparing the neural effects of estradiol in males and females are few, but in general, findings suggest different effects between the sexes on aspects of hippocampal plasticity and morphology. Whereas in ovariectomized rats estradiol and estradiol benzoate increase cell proliferation and cell survival in a duration-specific manner in the dentate gyrus (50, 591, 690), chronic and short-term administration of estradiol or estradiol benzoate in gonadectomised male rats do not (50, 591). In contrast, chronic testosterone or DHT (non-aromatizable to estradiol) increases hippocampal neurogenesis in gonadectomized adult rats (248, 591) as will be discussed below. Intriguingly, progesterone increases neurogenesis in male mice (690). Together, these findings suggest a greater influence of androgens (and perhaps progesterone) than estradiol on neurogenesis in males.

Like ovariectomy in females, castration in males reduces CA1 spine synapse density (372) but whereas estradiol ameliorates this effect in females, it does not in males (372). Instead, testosterone or non-aromatizable DHT ameliorated this effect in males (372). As in females gonadectomy reduces medial prefrontal cortical spine synapses in males, but estradiol benzoate has a more modest effect than DHT in ameliorating this reduction (236). The effects of androgens on hippocampal physiology and cognition in males is discussed in detail below.

Implications for Hormone Therapy (HT)

Aging is associated with declines in gonadal hormones in both men and women (362). Different cognitive domains show greater relative decline with aging, and these include long-term declarative memory, spatial learning, and executive functions (319). Spatial learning and memory deficits that occur across aging are exhibited across a number of species (70, 328, 524, 663-665). In women, cessation of ovarian functioning with menopause is associated with a decline in a number cognitive function in humans, non-human primates, and rodents (239, 357, 650, 651). A recent meta-analysis found that postmenopausal women perform significantly worse than pre- and/or perimenopausal women on delayed verbal memory tasks and phonemic verbal fluency tasks (651). In older postmenopausal women, higher serum estradiol levels are associated with better delayed verbal memory (139, 275, 670); but see (13), and less susceptibility to interference in an executive task, such as on the Stroop color word test. The frequency of mild cognitive impairment as assessed by the Mental State Examination Questionnaire (MMSE) is lower in women with higher serum estradiol and estrone serum levels after menopause (367). Longitudinal analysis also finds that older women with lower levels of bioavailable estradiol are at greater risk for significant decline on the MMSE (683). Such findings have led to interest in the use of estrogens via hormone therapy (HT) after menopause as a way to prevent or ameliorate age-related cognitive decline.

Indeed, in general estradiol attenuates age-related cognitive decline in a number of species (e.g., (208, 249, 276, 515). Nevertheless, the use of HT to ameliorate cognitive decline with aging has been controversial since the Women's Health Initiative Memory Study (162, 575) found no positive effect of Premarin therapy on cognition or risk for dementia. The WHIMS study had several crucial design flaws, including the advanced age of the participants and the use of an

estrone-based therapy (252, 253, 571). Thus, several reasons have been proposed to explain the different effects HT use has on cognitive functioning in postmenopausal women, including the critical period hypothesis (123) , the healthy cell bias hypothesis (83), and the formulation of HT (276, 540). On the latter point, meta-analyses have found that HTs composed primarily of 17-β estradiol show more beneficial impacts on cognition than do estrone-based HTs including Premarin (540). Perhaps relatedly, whereas women using estrogen therapy (ET) have larger hippocampal volumes compared to men and women who never used ET or used it in the past (382), CEE use in particular is associated with atrophy in the frontal lobe and hippocampus, although this effect is small (522). In addition to composition, age at HT initiation impacts outcome (539) and this has been termed the critical period hypothesis. It has been suggested that an earlier age of HT initiation, one that is closer to menopause, may be associated with better outcomes compared to a later age of HT initiation (after age 65; (276, 539). This "critical window hypothesis" of HT initiation will be reviewed further as it relates to hippocampal and prefrontal cortex functions and plasticity. Finally, the healthy cell bias hypothesis (83) holds that negative effects on cognition occur when HT is initiated after neurodegenerative decline has already commenced – that is, once cells and the brain are compromised. In addition to age, composition, and brain health, other factors likely moderate the effects of HT, including dosage, duration, administration route, and aspect of cognition assessed. These factors will be explored further below.

The Hippocampus and HT

The hippocampus is affected by age and demonstrates decreases modestly in volume with age in humans (519-521, 523). In rodents, the balance of studies indicate that hippocampal volume (323, 389); but see (188, 516) and cell number (632) do not decline with age. However, neurogenesis rates do decline with age in the rodent hippocampus (159, 262, 351). Furthermore astroglia in the dentate gyrus and CA1 region of the hippocampus in male mice show increased surface and volume with aging, suggesting regional remodeling of astroglia with age (528). Neuropil, synaptic density, and neurogenesis levels all decrease with age in humans, non-human primates, and rodents (160, 302, 374, 430, 523, 534, 589, 633). Further, the persistence of LTP, and LTP-related gene expression, also declines with age in the rodent (479, 541). For reviews on the effects of age on the hippocampus, see (140, 142, 534). There is a critical window for the effects of HT on cognition and hippocampal plasticity in animals (583, 639) and humans (125, 401). Acute 17β-estradiol injection increase cell proliferation in the dentate gyrus 1 week but not 4 weeks after ovariectomy, suggesting reduced responsiveness after removal of the ovaries (602). Consistent with a critical window hypothesis, the hippocampus becomes less sensitive to estradiol during aging: Cell proliferation in the dentate gyrus is upregulated by acute estradiol in young female rats (49, 107, 468, 469), but middle-aged nulliparous rats fail to show increased cell proliferation in response to estradiol (46, 107) or estrone (46). Further, estradiol administered to ovariectomized rats increases dendritic spine density in the apical region of CA1 pyramidal cells in young female rats but not in aged female rats (4). Interestingly, short-term, but not long-term estradiol benzoate increased spine density in the dentate gyrus of aged chronically ovariectomized multiparous females to levels typical of young rats even after chronic ovariectomy (431).

Reductions in the plastic response of the hippocampus to estradiol are accompanied by behavioral changes in response to HT and ovariectomy. Long-term treatment with estradiol after surgical menopause in middle age enhances spatial working memory in rats when treatment is initiated 3 months, but not 10 months, after ovariectomy (206). Whereas ovariectomy impairs spatial reference memory in young adults, it can enhance spatial reference memory in middle aged rats (48, 67) and does not seem to affect older female rats (601). Further, treatment with estradiol enhances reference memory of ovariectomized young and middle-aged females but does not improve performance of ovariectomized aged female rats (601). Estradiol benzoate treatment improves retention in the Morris Water Maze at different doses for young, middle-aged, and aged female rats (177). Specifically, middle-aged rats have best memory retention under low estradiol benzoate administration, and aged rats had best retention under a high dose of estradiol benzoate administration (177) . This pattern of results suggests that higher estradiol may be required at an older age to observe cognitive benefits in a hippocampus-dependent task.

In humans, HT effects on hippocampus-dependent tasks such as spatial working memory (146, 147) have been reported. However, meta-analysis finds that consistent effects of HT on visuospatial ability are not reliably detected (276). In non-human primates, tonic estradiol administration after ovariectomy improves performance compare to control treatment on the spatial delayed recognition span test, which is hippocampus-dependent (360). Cyclic estradiol replacement in aged rhesus monkeys improves delayed non-matching to sample task, also hippocampus-dependent, and delayed visual-spatial working memory (which also recruits the prefrontal cortex; (515). Thus, despite possible reductions in sensitivity to HT in later life, a number of species show benefits in terms of hippocampal-mediated cognition later in older age.

The prefrontal cortex and HT

The prefrontal cortex, like the hippocampus, is negatively affected by age. During normal healthy aging, there is a dysfunction of prefrontal cortex function in humans, non-human primates, and rodents (71, 180, 198, 268). Age-related cortical volume decline is more evident in prefrontal gray matter (orbitofrontal and dorsolateral prefrontal cortex) than other areas, including the hippocampus (518, 543). Further, it seems that cell death is unlikely to account, at least fully, for the prefrontal cortex volume changes occurring with aging, as several post-mortem histological examinations suggest preserved total numbers and densities of neurons in older compared to younger subjects even as cortical thickness decreases (445, 488, 489). Reductions in dendritic spines have been reported in layers 2/3 and 5 of the prefrontal cortex (489, 490). Finally, volume changes may also be the result of synapse loss in the prefrontal cortex observed with aging as has been found in humans, rats, and non-human primates (101, 148, 409); but see (552).

Estradiol supplementation following ovariectomy increased spine density in layer III of the dorsolateral prefrontal cortex, and induced a shift towards smaller spines in both young (Hao et al., 2007) and aged (249) rhesus monkeys. However, the nature of this plastic response is somewhat altered in old age, as ovariectomized untreated young females have more small spines than aged monkeys given estradiol (250). Thus, aging affects the responsiveness of the prefrontal cortex to estradiol (as is the case for the hippocampus). Consistent with a critical window of therapeutic efficacy, 17β-estradiol given immediately or 3 months after ovariectomy, but not 10 months after ovariectomy, enhanced delayed-match-to-position T maze performance (206). Furthermore, estradiol treatment in middle age immediately after ovariectomy, but not 5 months after ovariectomy, enhanced performance on the 5-choice serial reaction time task, which is prefrontal cortex-dependent (74). However, estradiol improved some aspects of spatial working memory in aged rhesus monkeys even after decades of estrogenic deprivation (360). Finally, it is worth mentioning that, in addition to age at administration, the benefits/detriments of HT may depend on a number of other factors, including whether menopause has been surgical or natural (3) and reproductive history (48).

Primate models of clinically-relevant HT regimens have found mixed results regarding prefrontally-mediated cognition, likely depending on whether or not progesterone was added to the HT. A recent study in aged ovariectomized rhesus monkeys found no positive effect of four chronic (range: 209 to 757 days) HT regimens (continuous E2 alone, and continuous or cyclic E2 with cyclic or continuous progesterone) on delayed responding, delayed non-match to sample, and object discrimination tasks (53). Indeed, continuous estradiol with cyclic progesterone impaired performance in an object discrimination task (53). In this study, hormone treatment was initiated 6-12 weeks after ovariectomy, behavioral testing began 1 month after HT initiation, and animals were tested on the battery over a 16 month span, while continuous HT was administered by pellet, and cyclic HT was administered by intramuscular injection every 28 days. The fact that in each of these HT progesterone was also administered may account for the failure to find a benefit of estradiol on cognition. Others (637, 638) have found beneficial effects of continuous estradiol treatment supplemented by estradiol valerate injections in aged ovariectomized rhesus monkeys tested on the Wisconsin Card Sort Task, a delayed matching-to-sample task, and a visual cued reaction time task; cyclic progesterone treatment did not alter this effect (618, 619). Spatial recognition memory was less sensitive than spatial recognition memory to HT (637), and delayed matching-to-sample task accuracy was modulated in a time-dependent fashion (with benefits seen at 12 but not 24 weeks following HT initiation, when tested repeatedly). Lastly, in

another study giving aged ovariectomized rhesus monkeys injections of estradiol cypionate every 3 weeks, performance improved substantially in a delayed response test of spatial working memory and modestly in a delayed nonmatch to sample recognition memory task (515). Thus primate models suggest that progesterone eliminates the positive effects of estradiol alone (continuous or cyclic) on a variety of cognitive tasks.

A meta-analysis (276) found that verbal memory shows consistent positive effects of HT. Previously, a meta-analysis found consistent improvement in frontally mediated concept formation with HT (527). HT administered to peri- or post-menopausal women also selectively reduced perseverative errors (prefrontal cortical-mediated executive function) in the California Verbal Learning Test (307, 322). Keenan et al., (322) for example, found that measures of executive function, but not memory more generally, were improved in a small sample of women taking HT (composition unfortunately not reported). Furthermore type of HT plays a role as verbal memory performance is better in postmenopausal women receiving 17β-E compared to CEE in a sample of women with risk factors for AD (680). Additionally, among postmenopausal women at risk for AD, 17β-estradiol use was associated with a three standard deviation advantage in verbal memory relative to women taking CEE (576).Thus, prefrontal cortex-mediated behaviors, inducing verbal memory are positively affected by HT dependent on type of HT, time since menopause and brain health status at the time of HT use. We will further discuss HT use in men and women at risk for AD at the end of this review. Next, we will review the effects of androgens on hippocampal and prefrontal physiology and function.

Androgens

In males, leydig cells in the testes are the major sites of production and release of androgens such as testosterone. In females, serum levels of androgens primarily originate from the ovaries. Additionally, the zona reticularis of the adrenal glands releases a weak acting androgen, dehydroepiandrosterone (1). In males, the testes produce androgens via a negative feedback mechanism signaled by leutenizing hormone (LH) released from the anterior pituitary. Similar to females, males also produce dehydroepiandrosterone that is released from the adrenal glands. Subsequent production of testosterone negatively feeds back on the hypothalamus (and other structures) to shut down the release of LH, a mechanism that relies upon binding to the androgen receptor (AR) (see below; (131). LH signals androgen production in the ovaries by binding to thecal cells to increase intracellular levels of cholesterol, but the majority of testosterone is converted to estradiol (89).

There are two major metabolites of testosterone that have biological activity: estradiol and dihydrotestosterone (214). Dihydrotestosterone (DHT) is metabolized from testosterone via the action of 5alpha-reductase. DHT is considered a more potent androgen as it binds with greater affinity to the AR compared to testosterone (365). Estradiol, the other major metabolite, is produced via the enzyme, aromatase, but once formed, estradiol acts upon the estrogen receptor (ER) (see above). Thus, when examining the effects of gonadal steroids such as testosterone upon physiology and behaviour, it has to be understood that testosterone can exert its effects through the AR and/or the ER (see Figure 6). Additionally, while DHT cannot be converted to estradiol, DHT can further be reduced to an active compound, known as 3β diol, which binds with high affinity to ER- β (478) and mimics the effects of estrogen in stimulating a number of different behaviors (442).

Testosterone and DHT are released directly into the bloodstream and carried to various tissues via androgen binding proteins, such as steroid binding globulin. Specificity of androgen's actions is achieved through the binding of the appropriate AR or ER. Although it is well known that the level of estrogens vary across the menstrual cycle in primates and estrous cycle in rodents, it is less well known that androgen levels vary in males. In men, androgen levels fluctuate diurnally (with higher levels seen in the morning), but also across seasons (81, 582).

Androgen Receptor

Like ERs, the AR belongs to the steroid receptor superfamily of ligand activated transcription factors. Besides the AR, this family of receptors contains a number of subfamilies,

such as glucocorticoid, mineralocorticoid, and progesterone receptors. The AR is located on the long arm of the X chromosome, near the centromere, at position Q11-12 (84, 390). The open reading frame is approximately 2757 base pairs (509) and contains 8 exons (390). The first exon codes for the amino terminus domain (NTD), which contains the activator functions (AF1 and AF2) important for interaction with other proteins (such as heat shock proteins which normally bind to keep the AR inactive); exons one and two code for the DNA binding domain (DBD), with the last five exons coding for the carboxy terminus in which the hinge region and ligand binding domains (LBD) are located (203). The structure of the AR is highly conserved among mammals with homology of the DBD and LBD well conserved from frogs to humans; the DBD itself is 100% identical between rats and humans. However, the NTD is highly variable among species, and this is likely the reason the protein functions distinctly in different species (203). Moreover, this NTD contains a variable number of the amino acid sequence, CAG, which codes for a glutamine. Abnormal expansion in the number of glutamine repeats results in inherited forms of neuromuscular disease such as Kennedy syndrome and spinal and bulbar muscular atrophy (203). Furthermore, the number of glutamine repeats may be related to androgen levels and cognitive impairment observed in Alzheimer's disease (see below).

AR Distribution in the Hippocampus and Prefrontal Cortex

Hippocampus: CA1/CA3/DG

The hippocampus is a target for androgens as the CA1 and CA3 express robust and moderate levels, respectively, of AR immunoreactivity in males and females of all rat strains examined to date (87, 248, 681). Except for the Wistar strain (12), AR immunoreactivity is completely absent in the dentate gyrus of male and female rats (248, 681). Overall, similar patterns of AR distribution have been observed in the hippocampus of male and female mice (517). AR messenger RNA is reportedly expressed in the CA1 region of both adult men and women (62), as well as in CA3 pyramidal neurons of post mortem subjects of unknown sex (610). While AR immunoreactivity is typically nuclear, several regions in the adult hippocampus of male rats are observed to display non-nuclear AR immunoreactivity (171, 348). For example, axons, dendrites, and thorny excrescences (specialized structures near the soma of pyramidal neurons) in the CA1 and CA3 regions have been reported to contain presumptive AR immunoreactivity in rats (599). In the region adjacent to the subgranular zone of the granule cell layer, AR immunoreactivity is reported in the stratum pyramidae and infragranular layers in rats (599). AR immunoreactivity is noticeably absent in new adult born granule cells in the dentate gyrus in rats and mice (247, 517), suggesting androgens regulate adult neurogenesis via a cell non-autonomous mechanism (191, 248). In terms of the expression of ARs in males and female mice, the intensity of the signal tends to be lower in females compared to males, likely owing to the scarcity of androgen production in females compared to males (388).

Prefrontal Cortex

The prefrontal cortex is also a target for androgens as cells display AR immunoreactivity in monkeys and rats, but there are some important species differences. Finley and Kritzer (171) reported all six layers of the dorsolateral and orbital regions of the prefrontal cortex of both male and female rhesus monkeys contained intense nuclear AR immunoreactivity. A large number of AR immunoreactive cells colocalized with neuron-specific enolase (NSE) and glial fibrillary acidic protein (GFAP), suggesting ARs are expressed in both neurons and glia, respectively. A small portion of AR expressing cells are also colocalized with an oligodendrocyte marker, in contrast, however, there was no overlap of AR immunoreactivity and a microglia marker (MRC OX-42). Similarly, a large majority of AR immunoreactive cells in the cerebral cortex, which includes the frontal cortex, of adult male rats are neurons (383). Aubele and Kritzer (2012) describe dense nuclear AR immunoreactivity with light cytoplasmic staining in pyramidal neurons of the cingulate cortex and multipolar neurons in the septal nucleus of the medial prefrontal cortex (30). In contrast to monkeys, however, few if any AR-expressing cells are glia in the adult rat male cerebral cortex (138). Developmentally, however, cells positive for AR and GFAP expression were observed in the prefrontal cortex of ten day old male rats (138). Thus, while it appears ARs are expressed in a heterogeneous mixture of cells in the prefrontal cortex of non-human primates,

expression is more homogeneous in the rat with only neurons displaying AR immunoreactivity.

Androgen Receptor Signaling

The accepted model of androgen receptor action entails the binding by testosterone or dihydrotestosterone and causing a conformational change of the receptor (see Figure 7). This conformational change allows the ligand bound receptor to dimerize with other bound ARs, removing the inhibitory heat shock proteins that serve to normally keep the protein inactive. The dimer is then transported to the nuclear compartment where it interacts with the chromatin at androgen response elements (AREs) to initiate the transcription of androgen responsive genes. The ARE sequence is suggested to be 5'GATCAT**AGTACGTGATGTTCT**CAAGATC-3' (core recognition sequence is bolded) as determined by gel mobility shift assay and mutation analysis (132), however, this is far from conclusive as other ARE's have been identified (221). The binding of the AR complex to an ARE is important for initiating transcription via activation of an RNA polymerase, and for recruiting other proteins to amplify testosterone's effects on protein production. Multiple target proteins have been reported to be under regulation by androgens, such as the two enzymes important for converting testosterone into active metabolites (DHT and estradiol), 5α-reductase and aromatase (316), and the AR itself (326). A recent DNA microarray study compared gene expression in the hippocampus of castrated and sham-castrated males (510). Of the genes that were down regulated following castration, most were involved in intracellular signaling and cell survival, but also genes important for plasticity (510).

This accepted model of androgen action outlined above is termed a 'classical genomic response' and can take several hours before protein production is achieved. However, while less studied, non-classical/non genomic responses have been reported to exist for the AR (166). Revelli et al (526) suggest androgens act non-genomically when they occur rapidly (from seconds to minutes), essentially ruling out the possibility of mRNA production. Androgen treatment increases the intracellular concentration of Ca++ via regulation of a voltage sensitive Ca++ channel that results in the activation of protein kinases (526) and may induce the transcription of a number of proteins that do not contain a traditional ARE (512).

ARs are typically observed in the nucleus of a cell and, in general, are thought to mediate the classic genomic effects of androgen action (but see below for exceptions to this). However, AR expression is observed in non-nuclear locations, such as in dendrites or axons, and is suspected to mediate the non-genomic effects of androgens. To date, regions in the forebrain, the entorhinal cortex, and the hippocampus are known to express these extra nuclear ARs (137, 138, 599).

Androgen-mediated Structural Plasticity in the Prefrontal Cortex

The prefrontal cortex and hippocampus of mammals display plasticity in adulthood and while androgens mediate these changes in male and female rodents, estradiol does play a small role (as reviewed below). Hajszan et al. (236) reported that castrated wild type males displayed a decrease in the number of spine synapses in the mPFC. However, systemic injections of 200 µl of dihydrotestosterone over two days reversed this decrease with the density of spines increasing by 136% and restoring the number to sham levels. Interestingly, 10*µ*l estradiol administration also increased the number of spines, but only to a limited extent (56% increase) compared to dihydrotestosterone. The contribution of ARs to the ability of dihydrotestosterone and estradiol to increase spine density in the mPFC was previously investigated using testicular feminized mutation (TFM) male rodents. TFM males are chromosomally XY but harbor a mutation in the gene encoding the AR that results in androgen insensitivity (reviewed in (246). The number of synaptic spines in the mPFC of Tfm affected male rats was lower compared to intact wild type males. Gonadectomy of TFMs decreased spine levels to gonadectomized wild type male levels, but there was a difference in the ability of dihydrotestosterone and estradiol to restore these levels: While dihydrotestosterone was effective in increasing spine levels by 63%, estradiol was far more effective and increased levels 123%. It is counter-intuitive that an androgen increased spine levels in the *androgen insensitive* Tfm males, but dihydrotestosterone is further reduced to compounds that bind both estrogen receptors and GABA-a receptors. Alternatively, the mutant Tfm AR does maintain some ability to bind androgens, but TFM affected males do not display transcriptional activity at physiological androgen levels (365), and thus this is likely not a viable

option to explain the results. Beyond the notion that DHT is reduced to compounds that bind different receptors, another suggestion is that the structural plasticity observed in the TFM affected males following dihydrotestosterone treatment may be mediated by non-genomic actions of the AR. Reports indicate that androgens regulate the mobilization of intracellular calcium and affect firing rates of neurons (see below), two processes known to affect structural plasticity.

Androgen induced spine synapse formation has also been observed in layer I of the prefrontal cortex of non-human primates. Male gonadectomized St. Kitts vervet monkeys displayed fewer spines compared to intact males (237). In females, the number of spines was also reduced following ovariectomy, but the density was increased in ovariectomized females treated with testosterone (237). Unfortunately, there is no data documenting the ability of androgens to affect spine density in these gonadectomized males, but it does seem possible given the results in females. Thus while there are limited studies, testosterone acting via AR (and ER to some extent) increase spine density in the mPFC of male and female rodents and primates. While it does not appear there is a sex difference in expression of ARs in the prefrontal cortex, the difference in serum androgen levels may produce sex differences in behaviours mediated by this region of the brain.

Androgen-mediated Structural Plasticity in the Hippocampus

Androgens also regulate a number of structural changes in the hippocampus of both males and females. As described above, Woolley et al. (672) reported that the number of apical dendritic spines of CA1 pyramidal in females was affected by the estrous cycle. Females in proestrus had the highest number of spines compared to females in diestrus and to gonad intact males. Leranth et al (372) reported that gonadectomy of males decreased the number of apical spines on CA1 pyramidal neurons (see also (342), an effect that was reversed following systemic treatment of either testosterone or dihydrotestosterone. Surprisingly however, estradiol did not have an effect on the density of spines in males, unlike in females. In females, estradiol modulated spine density in the apical region of CA1 pyramidal neurons compared to males. Ovariectomy reduced the number of spines in the apical region of CA1 pyramidal neurons, whereas estradiol treatment reversed the loss of spines in ovariectomized females unlike in males. Furthermore both testosterone and dihydrotestosterone treatment separately restored spine density to normal levels in adult female rats. However, it was noted that dihydrotestosterone did not affect spine formation to the extent of testosterone, which is perhaps surprising given that dihydrotestosterone is the more potent androgen. Thus, it appears that male rats rely upon androgen signaling to maintain spine density, but females rely upon both androgenic and estrogenic signaling to maintain spine density in the apical CA1 region of the hippocampus. In non-human primates, testicular hormones modulate spine density of male St Kitts vervet monkeys. Castration reduced spine density in the CA1 region and the dentate gyrus, and to a lesser extent the CA3 region, compared to intact controls (421). Thus, taken as a whole, androgens affect synaptic connectivity in the hippocampus of male and female rodents and in male non-human primates.

While the above studies suggest androgens affect spine density in CA1 pyramidal neurons via genomic effects (males were treated for 2 days), this has remained largely untested until recently. Using isolated hippocampal slice preparations from adult males, Hatanaka et al (255) observed rapid effects of androgen treatment on spine formation in apical CA1 pyramidal cells. Surprisingly, spine density was increased following 0.5 to 2 hours of treatment with either testosterone or dihydrotestosterone. Spine formation was blocked when slice preparations were treated with either androgen in the presence of inhibitors for protein kinase A or C, as well as mitogen activated protein kinase (MAPK). Finally, rapid generation of spines in CA1 pyramidal cells was also blocked when slices were incubated with the AR specific antagonist, hydroxyflutamide. These data imply, then, that androgens increase plasticity in CA1 pyramidal neurons via a rapid, non-genomic effect through AR mediated activation of intracellular pathways that converge on MAPK.

Structural plasticity in the CA3 region of the hippocampus is also modulated by androgens (256). Similar to the effects of testosterone and dihydrotestosterone on CA1 pyramidal neuron spines, androgen treatment increased the production of thorny excrescences within two hours of treatment. Generation of these structural modifications were also blocked in the

presence of hydroxyflutamide and MAPK inhibitors, again implying androgens rapidly induce thorn generation via an AR mediated increase in MAPK activity. These thorns are also important in terms of connectivity with newly added neurons in the dentate gyrus. Adult born cells in the dentate send projections to CA3 pyramidal neurons within 4 to 10 days after proliferation and contact these special thorn structures (254). Destruction of the CA3 region results in a decrease in neurogenesis in the dentate gyrus, suggesting this region is an important mediator promoting neurogenesis (380).

As stated above, androgens regulate neurogenesis in the dentate gyrus, likely via a non-cell autonomous effect as newly born neurons to not express ARs (248). The majority of studies support the conclusion that proliferation of cells in the adult dentate gyrus is not affected by gonadectomy or androgen replacement (95, 248). Instead of affecting neurogenesis via proliferation, studies suggest androgens increase cell survival (248, 591); see above for a description of the stages of neurogenesis).

Castration results in a decrease in the number of surviving BrdU-labeled cells in the adult dentate gyrus compared to sham castrates (591). Males castrated and treated with testosterone or dihydrotestosterone displayed increased survival of BrdU-labeled cells, but estradiol did not have a significant effect on neurogenesis, suggesting an AR mediated mechanism to promote neurogenesis. We directly tested this hypothesis in castrated wild type males or TFM males treated with Silastic capsules containing either testosterone or were empty (248). The wild type males given testosterone displayed more BrdU-labeled cells compared to blank treated controls. However, the TFM males did not display an increase in neurogenesis even after one month of treatment with testosterone. To provide complimentary evidence to further implicate an AR mediated mechanism, we castrated wild type males and treated them with dihydrotestosterone or a combination of dihydrotestosterone and flutamide (an AR specific antagonist). While one month of systemic treatment with dihydrotestosterone increased neurogenesis, this increase was blocked in males given a combination of dihydrotestosterone and flutamide. Together, these studies provide convergent evidence that androgens act directly through the AR to increase neurogenesis in the dentate gyrus of adult male rats. Surprisingly, though, ARs are not expressed in new adult born cells in the dentate gyrus, implying a non cell-autonomous survival mechanism is initiated by androgens somewhere else in the brain to increase survival in the dentate gyrus.

The degree to which androgens affect survival of new cells in the adult hippocampus is partially dependent upon the length of treatment. Brannvall et al. (87) reported five days of treatment with the androgenic anabolic steroid, Nortestosterone, decreased the production of new neurons in the dentate gyrus of male and female rats by approximately 75%. However, 15-21 days of androgen treatment was reportedly insufficient to affect the survival of BrdU labeled cells in male rats (94, 592), suggesting at least a minimum of 22 to 30 days of chronic androgen treatment is necessary for survival of these cells.

Thus, the preceding studies show that castration during adulthood reduces survival of new neurons in the DG of rodents. However, results in non-human primates appear to reveal a different role for androgens in neurogenesis. Castration before puberty in rhesus macaques results in an increase in the survival of cells in the hippocampus (12), suggesting androgens normally *decrease* cell survival in pre-adolescent mammals compared to adulthood. However, in this study castrates were housed together, with the intact males kept in a separate area, thus it is possible that living in a troop with a dominance hierarchy in which subordinates display increased anxiety may have also negatively affected survival of new neurons.

Several important conclusions can be drawn from the above studies. Androgens appear to affect structural plasticity of the hippocampus and prefrontal cortex of both males and females, although sex appears to be an important factor in the degree to which androgens facilitate structural changes in the hippocampus. In terms of the production of structures important for synapse formation (i.e., dendritic spines and thorns), androgens positively mediate establishment on a very short times scale (minutes to hours) through the stimulation of MAPK, suggesting a non-genomic effect of androgens on plasticity. Given that a protracted time frame is necessary before neurogenesis is affected by androgens in rodents (i.e., beyond 21 days of androgen treatment), we suspect androgens are acting via a classic genomic response to change adult hippocampal neurogenesis rates. The exact nature of androgen's involvement in mediating neurogenesis in non-human primates is not explicitly known, as the interaction of the stress and

gonadal axes may have obscured the mechanism. Finally, androgens appear to mediate both genomic and non-genomic effects through the AR, but engage both cell autonomous (structural reorganization in CA1 and CA3) and cell non-autonomous (neurogenesis in the dentate) mechanisms.

Androgens and Spatial Memory in Rodents

As outlined above, androgens influence structural plasticity in the prefrontal cortex and hippocampus, which suggests androgens influence the function of both areas. However, while it is clear estrogens regulate cognition, there is a limited amount of research conducted on the role of androgens, which we review below.

Spatial Reference Memory

Studies reveal androgens do not affect the learning or acquisition of the standard reference memory version of the Morris Water maze task, but they may influence short-term spatial reference memory in this task (546, 590, 591). For example, neither castration (56, 546, 591) nor replacement with various doses of testosterone over 7-15 days (590) of rats and mice significantly affected acquisition when tested in the Morris Water Maze. However, castrated male rats systemically treated with one of two doses of testosterone (.25 and 1mg) increased spatial memory retention (assessed via a probe trial) if given for 7 but not 15 days, suggesting short-term improvement with testosterone. When the location of the hidden platform was moved to a new location within the water maze, males given .25 or 1mg of testosterone showed perseveration in the quadrant where the platform was previously located. This suggests that low dose testosterone improved reversal learning, but that higher doses of testosterone impaired the shift from learning the old location to the new location, which is indicative of an effect of androgens on prefrontal cortex dependent learning. Overall, androgens appeared to affect components of spatial memory and reversal learning, and these depended upon the dose of androgens.

In adulthood, males consistently display superior spatial acquisition in the Morris water maze compared to female rats (309), suggesting a role for gonadal steroids in the regulation of this sex difference in spatial memory. Androgen insensitive TFM male rats displayed deficits in the reference version of the water maze when compared to males during the late phase of acquisition (310). While performance was similar to gonad intact wild type females at this time point, successive sessions revealed masculine performance of the TFMs such that they performed in a similar manner to the wild type males. These results suggest ARs may play a role in the acquisition of spatial memory, especially in the early phase of testing. Interestingly, two studies have observed deficits in acquisition and spatial memory retention in adult gonad intact males infused with the AR antagonist, flutamide, directly into CA1 region (150, 454). Deficits were only observed when flutamide was administered immediately pre- or post-training, but not when administered 2 hours post training (150), suggesting that flutamide interfered with protein synthesis needed for memory retention. Taken together, these studies imply androgens enhance spatial navigation performance in the Morris Water Maze may act upon ARs expressed in CA1 region.

In order to examine developmental effects of androgens on spatial ability, authors have manipulated perinatal gonadal steroids levels to determine the contribution of organizational effects of gonadal hormones on sex differences in spatial ability in adulthood (291, 660). Masculinization of female rats with testosterone injected shortly after birth resulted in similar performance in the water maze compared to normal males when later tested in adulthood. Furthermore, feminization of males, via injections of the AR antagonist, flutamide, perinatally resulted in female-like performance compared to normal males and masculinized females. Superior spatial performance was related to the masculinization of structures in the hippocampus as the area and size of somata in the CA1 pyramidal layer were larger in males and females treated with testosterone and estradiol, but not dihydrotestosterone (291). Androgens, but not estradiol, masculinized area and somata size in CA3 pyramidal cells. Given that males display a perinatal surge in testosterone, but females do not (657), indicates this early developmental period as potentially important for the masculinization of spatial reference memory ability in adulthood.

Spatial Working Memory

Gibbs (207) employed a delayed matching-to-place version of the T-maze to examine spatial working memory in male rats. Castrated males given treated with normal to supraphysiological levels of testosterone produced fewer errors on this task (207, 350), whereas males treated with estradiol (5mm capsule) learned the task faster than other groups. Utilizing a delayed non-match to place strategy, Hawley et al (258) examined spatial working memory in the Y maze in males castrated and implanted with capsules that produced low or normal physiological levels of testosterone. Memory retention was only facilitated in males systemically treated with physiological levels of testosterone if the delay was extended to 48 hours; shorter delays did not reveal a difference between the testosterone or vehicle treated groups. Using a relatively simple task that does not require food deprivation, McConnell et al (416) examined performance in the object memory location test (OMLT), which takes advantage of the tendency of males to explore objects located in novel spatial locations. Intact, estradiol, or testosterone-implanted males spent more time investigating the object in a novel location compared to the gonadectomized males. Collectively these studies suggest that testosterone can positively influence spatial working memory in male rodents.

Edinger et al (152) utilized an inhibitory avoidance task to assess the effects of androgens on spatial working memory. The hippocampus plays a role in the inhibitory avoidance task (17, 385), but other regions such as the amygdala are also involved in the encoding and expression of the spatial location of where a shock was administered in this task (293). Castrated males spent less time freezing compared to intact males and castrated males treated with testosterone or dihydrotestosterone, signifying androgen treatment enhanced memory. Collectively these studies reveal that testosterone, acting via both the AR and ER, can facilitate spatial working memory in males. In general, several important conclusions can be drawn from the rodent studies discussed above. Androgens act developmentally and in adulthood to mediate spatial working memory via AR and ER signaling, but to a lesser extent affect spatial reference memory via the AR exclusively.

Androgens and Spatial Memory in Humans

Androgens also influence spatial ability in humans. Cherrier et al (104) examined spatial reasoning (Complex Design Construction), spatial navigation (Puget Sound Route Learning Test) and visual working memory (Subject Ordered Pointing Task; SOPT) in men undergoing combined flutamide and leuprolide treatment, a regime designed to deplete androgen signalling in order to combat metastatic prostate cancer. Men maintained on androgen deprivation therapy for 3 months displayed performance deficits, such as fewer completed complex design construction and increased pointing errors on the SOPT. These results imply performance deficits in spatial reasoning and working memory were due to low androgen levels. However, the results are not as easy to interpret as serum estradiol levels were also comparably low at 3 months of androgen deprivation therapy and thus it is not known if deficits in performance were due to loss of AR or ER signalling.

Similarly, healthy older men treated with weekly injections of testosterone enanthate displayed superior performance in the Route test, a spatial navigation task that measures the ability of individuals to traverse a short route within a room (103). Testosterone treatment improved block design completion scores, but this effect was only observed at 6 weeks of treatment. O'Connor et al (462) examined similar spatial tasks in young, hypogonadal men treated with either 200mg of Testosterone enanthate two times per week versus a group of hypogonadal men treated only once per week. Testosterone treatment raised serum levels comparable to Cherrier et al (83), however, bi-weekly testosterone enanthate injections decreased performance on the block design task, suggesting spatial memory was negatively affected in this young cohort of males. Taken together, these two studies imply androgens affect spatial performance in an age, and possibly dose, dependent manner. It is possible, though, that with age comes a greater deficit in spatial abilities and androgen replacement therapy is able to improve performance following an age related decline.

Studies examining relationships between androgen levels in healthy men and women have found that testosterone levels are related to spatial ability. Driscoll et al (141) found men

performed better in a virtual water maze compared to females, an advantage that persisted in the aged male group, and a finding that mimics the animal literature. The authors reported a positive correlation between salivary testosterone levels and spatial performance in males only, suggesting the sex difference in advantage may be related to testosterone levels. Further to this, Gouchie and Kimura (219) dichotomized men and women into low testosterone or high testosterone using a median split and subjected participants to a number of paper and pencil spatial tasks, including the paper folding task. In men, low testosterone was associated with better performance compared to the high testosterone group whereas the relationship was reversed in women as the high testosterone women scored better than the low testosterone women. These studies collectively suggest there are sex differences in the relationship between testosterone and performance on spatial abilities. Thus, just as there is for estradiol, testosterone may facilitate spatial memory at an optimal level in humans.

Female-to-male (FM) transsexuals receive androgen therapy as part of their regime for sex reassignment surgery and this population offers a rare chance to systematically examine the adult effects of androgens on spatial skills. Based on these studies, it is clear that there are effects of androgen treatment on cognitive functioning. Before androgen treatment, FM transsexuals displayed the typical female performance on spatial and verbal fluency tests (581, 625, 626). Androgens improved performance on spatial memory tests, but verbal fluency decreased when cognitive performance was compared to baseline levels following three months of androgen treatment. Interestingly, the testosterone enhancing effects lasted well after hormone therapy was discontinued (581). Thus, FM transsexuals developed the typical pattern of male superior performance in spatial tasks while subsequently losing their female verbal superiority as they transitioned from female to male.

While serum levels of androgens have typically been used to indicate androgen sensitivity, as reviewed above, few studies have directly examined the role of the AR in cognitive behaviours. The number of glutamine repeats (CAG) in the amino terminus dictates the ability of the AR to respond to androgens (98). When androgens bind to the AR, they cause a conformational change, and the degree to which androgens cause this change can be utilized as an indication of androgen sensitivity. Typically, the amino terminus contains around 20 CAG repeats, with a wide variety being observed (211). Fewer CAG repeats results in increased sensitivity to androgens, whereas an expanded number of CAG repeats results in a receptor that is relatively insensitive to androgens (211). As stated above, androgens are released from the Leydig cells in the testes of males and production is regulated via a negative feedback mechanism (422). When the AR contains fewer repeats, androgen levels are low due to increased activity of the negative feedback system (93, 346). However, when the AR contains an expanded number of CAG repeats, the receptor does not bind androgens with high affinity, resulting in less negative feedback, and a subsequent rise in serum testosterone (93, 346).

CAG polymorphisms have received little attention in the literature, but one study suggests the number of repeats increases as men age (433). Two studies have examined cognition in relation to CAG repeats in men. Yaffe et al, (682) tested performance on measures of short term memory and attention (Trails B and Digit Symbol) in a large cohort of aged males. However, an increased CAG repeats was also inversely related to scores on the Mini-Mental Status Exam (MMSE), suggesting increased CAG repeat length may result in cognitive impairment. In the same cohort of men, Yaffe et al (684) correlated the levels of serum testosterone and estradiol with scores on the Trails B, Digit Symbol, and MMSE. There was a positive relationship with performance on all three tests and testosterone, whereas performance was negatively related to estradiol levels. Thus, the data suggest higher levels of testosterone are associated with better cognitive performance, but estradiol is associated with worse performance in aged men.

While the majority of studies outlined above utilized men, there are a few studies examining the efficacy of androgens to improve cognitive functioning in women (129, 130, 501). Postma et al (501) analyzed spatial cognition in women administered a single oral dose of testosterone, which resulted in improved placement accuracy compared to placebo when a 3-minute delay was introduced. Thus, it appeared androgens had an activational/adult effect and provided some savings when recall was delayed. Androgens were administered 4 hours prior to the start of the trials and thus it is very difficult to determine if testosterone was acting in a non-genomic manner. However, it has been shown that this dose of oral testosterone increased

serum values within 15 minutes and returned to basal levels within 90 minutes in women (617). Age appears to be a factor, as healthy postmenopausal women did not benefit when treated with testosterone undecanoate (40mg/day) in terms of verbal fluency, verbal memory, or spatial ability (336). This is in contrast to Cherrier et al (103) that found testosterone could improve spatial memory in healthy aged males (see above). There are some important differences to note that may have contributed to the incongruent findings. The ester attached to testosterone was different in each study (undecanoate in the postmenopausal study versus enanthate in the aged males), as was the route of administration (oral in the postmenopausal study and systemic injections for the aged male study). As a result, the serum testosterone values in Cherrier et al was approximately 45 nMol/L but was 2.3 nMol/L in the postmenopausal study. Thus, differences in performance may be a function of the dose, which was far lower in the females. Other studies find positive effects on verbal learning and memory in postmenopausal women using transdermal testosterone (129, 130), indicating exogenous androgens can be associated with improved verbal memory in women.

Estrogens and Androgens and Alzheimer's Disease

Alzheimer's disease is the most common type of progressive dementia in the elderly, and is characterized neuropathologically by β-amyloid deposits, neurofibrillary tangles, and neuron loss (564). The CA1 region of the hippocampus is one of the first brain areas to show atrophy with Alzheimer's disease, and CA1 volume is correlated with memory and dementia risk (23, 29, 551). Further, alterations in neurogenesis are linked to cognition and Alzheimer's disease (304, 305), suggesting deficits in cognition may be partially attributable to aberrant plasticity in the dentate gyrus. The prefrontal cortex is also vulnerable to neurodegeneration in both healthy aging and Alzheimer's disease; by the end stage, there is significant synapse loss in the prefrontal cortex, which correlates with the degree of global cognitive impairment (134).

The prevalence of Alzheimer's disease is two to three times higher in women, and this is not fully accounted for by longevity or level of education (18, 21, 285, 373). Once diagnosed, women display a rate of cognitive decline that is steeper compared to men (8, 616). There is evidence to link androgens to Alzheimer's disease in men. Lower serum values of testosterone are observed in men with presumptive Alzheimer's disease, and intriguingly, values were reportedly lower 10 years prior to a diagnosis (438). Expression of ARs is reduced in the basal forebrain of Alzheimer's disease patients (292). Furthermore, AR transcriptional activity is higher (due to fewer CAG repeats in exon 1 of the gene) in males with Alzheimer's disease compared to healthy controls and may be a causal factor in the observed decreased androgen production in men eventually diagnosed with the disease (370) Taken as a whole, evidence suggests a neuroprotective role of androgens in men with Alzheimer's disease. Taken as a whole, the sex difference in disease incidence and the decrease in androgens prior to disease onset in men strongly suggests gonadal steroids play a neuroprotective role and may be involved in the pathoetiology of Alzheimer's disease when serum testosterone levels are depleted. Results in animal models of Alzheimer's disease implicate androgens in regulating neuropathology. For example, depletion of endogenous androgens via gonadectomy increased Aβ plaque formation in the hippocampus, and other areas, an effect that was prevented by the treatment with testosterone or DHT (531). Gonadectomy also impaired hippocampus-dependent cognition in the 3xTg-AD male mice when tested in the Morris Water Maze, but performance was rescued following DHT treatment (531).These studies also suggest a novel treatment option to combat the decline in cognition. Indeed, memory in men with Alzheimer's disease or mild cognitive impairment is improved after treatment with testosterone (105) and a recent randomized control trials in postmenopausal women have shown improvements to cognition with testosterone treatment (274) paving the way for more research into this promising area.

Whereas androgen levels are associated with Alzheimer's risk and progression in men, estrogen levels are associated with Alzheimer's risk and progression in women (283, 406, 557). Having lower estradiol levels in older age is associated with increased risk for Alzheimer`s disease in women (283, 406, 557). Patients with Alzheimer's Disease have significantly lower estradiol levels but not serum estrone compared to normal controls (406). These results were not replicated, though, as others (121) have found higher serum levels of estrone, but not estradiol, among women with Alzheimer's disease compared to controls. Several studies have suggested

that hormone therapy is associated with lower risk of Alzheimer's disease among postmenopausal women (320, 477, 604, 688). Further, a number of clinical trials have indicated that estrogens can improve the cognitive and daily functioning of women already diagnosed with Alzheimer's disease (27, 170, 464, 622, 658). However, the effects of hormone therapies vary across studies, e.g., (447, 575, 646) and this is likely due in part due to different compositions of estrogens. Notably, the Women's Health Initiative Memory Study showed that conjugated equine estrogens (CEE) plus medroxyprogesterone acetate increased dementia risk in women over age 65, whereas the effects of CEE alone did not reach statistical significance (575). As previously discussed, meta-analysis has found that HTs composed primarily of 17-β estradiol have more beneficial impacts on cognition than do estrone-based HTs including Premarin outside the context of dementia (540). Hormone therapy composition likely impacts cognitive outcome among women with Alzheimer's disease, too. For example, among women with risk factors for Alzheimer's disease, verbal memory performance is better in women taking 17-β estradiol compared to CEE (576, 680).

Estradiol treatment may improve cognition in part through its neuroprotective effects and by decreased brain amyloid levels. For example, estradiol also has neuroprotective effects against oxidative stress and amyloid toxicity (see (82, 199) for a review) and reduces plasma amyloid β-40 levels in women with Alzheimer's disease. Finally, women with a history of hormone therapy use are associated with lower baseline amyloid β-40 levels in serum (35). However, the efficacy of estradiol neuroprotection in women may be affected by genetic background. Possessing the *APOE4* allele is a well-established risk factor for susceptibility to non-familial Alzheimer's Disease (26), and a lower age of onset and higher risk of Alzheimer's disease (73, 313, 423). There is a greater risk for Alzheimer's disease in women with *APOE4* compared to men (61). Hormone therapy interacts with genetic background, as women specifically without an *APOE4* allele have improved mood and cognition with estradiol-based hormone therapy (622). Consistent with an interaction between genetic background and estrogen exposure, Geerlings (201) found in a prospective study that longer reproductive period (age from menarche to menopause) increases the risk of developing dementia particularly for women with the *APOE4* genotype. These studies suggest that factors that alter estrogen exposure interact with pre-existing genetic risk for Alzheimer's disease, and that hormone therapy may alter cognitive decline differently depending on genetic background.

Conclusion

Gonadal hormones modulate forms of hippocampus-dependent and prefrontal cortex-dependent learning and memory in adult rodents, non-human primates, and humans. It is important to bear in mind that age, sex hormone type, and sex also modulate the relation between gonadal hormones and cognition. The modulation of prefrontal and hippocampal function, in the context of organizational sex differences in the central nervous system, affects the manifestation of sex-favoring cognitive abilities in verbal and spatial memory. Thus, we adopt the position, similar to others (53), that in addition to the organizational effects of sex hormones, analysis of factors affecting sex differences in adulthood is important for understanding cognition, neural mechanisms, and treatment for neuropsychiatric disease.

Despite a scientific climate in which understanding sex differences is increasingly emphasized, there continues to be a relative lack of studies examining sex differences in neural and cognitive outcomes of hormone treatment. However, a careful study of sex differences also requires more than simple comparison of men and women, or male and female rodents. Currently, the general practice has been to use sex as a covariate if there are no main effects of sex; however, there may be interactions with sex and other variables that need to be explored and are lost with the use of a covariate. Thus, a concerted effort in the scientific community is needed to not only test males and females but to use sex as a factor of interest rather than as a covariate in these analyses. Furthermore, care must be taken to record variables such as estrous or menstrual cycle phase that cause within-sex or within-subject variability. This may be particularly important when examining measures that involve the hippocampus or prefrontal cortex.

Variations in estrogens are associated with changes in synaptic plasticity, long-term potentiation, receptor levels and spine density in the hippocampus and other regions. There are significant but subtle differences in cognitive performance across the menopausal transition and perhaps to a lesser degree across the menstrual cycle. Despite a conception that men are devoid of fluctuations in testosterone, men show dramatic alterations in testosterone levels across the day and with increasing age. These alterations in levels of testosterone may be associated with variations in cognitive performance in men. It is also important to recognize that sex and sex hormones likely interact with genotype and experience to alter cognition in men and women in ways that have been underexplored.

In conclusion, estrogens and androgens can differentially impact specific forms of spatial and verbal memory based on age, sex, dose and task demands. Hormone treatment has promise for reducing or preventing cognitive impairment associated with aging and neuropsychiatric and neurodegenerative conditions. However, caution is warranted, as the factors that moderate cognitive outcome of hormone therapy (e.g., reproductive factors, genetic factors, hormone therapy composition) are currently not fully understood, and some hormone therapy compositions have negative health consequences such as cancer-promoting effects. As scientific recognition of sex differences in neuropsychiatric and cognitive disorders grows, it is hoped that a discussion of the role of sex hormones in cognition may contribute to the development of new, tailored therapeutic advances to promote healthy aging. In closing, we add our voice to the growing recognition that sex matters for brain health and that sex hormones can modulate cognition and hippocampus and prefrontal cortical morphology and function.

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Figure Legends

Figure 1.Tasks Favouring Women or Men. On average women show superior performance in tasks requiring perceptual speed, verbal fluency, visual memory and fine motor skills compared to men. However, men tend to do better than women on spatial tasks such as the Mental Rotations Test, the Paper Folding Test, and Embedded Figures and have better target accuracy even when accounting for sports history. Figure adapted from Figures 1 and 2 with permission from Kimura 1992 (330).

Figure 2. Morris Water Maze Task Theoretical data arising from male and female rodents in the Morris Water Maze task. The Morris Water Maze Task is a hippocampus dependent task that is widely used to study spatial learning and memory. Typically in the reference memory version of the task, animals learn the location of a hidden platform located just beneath the surface of the water, over successive trial days, in the context of extra maze cues located around the room. Before the location of the platform is learned, animals take longer and swim a greater distance to find the platform, but once the location is encoded to memory, animals typically swim directly to the platform when placed in the maze. Males typically outperform females on the reference version of this task in a variety of rodents (192, 660). Intriguingly performance is disrupted in females when landmarks (extra maze cues) are disorganized while male performance is disrupted when changing the geometrically positioning of the room compared to the maze (i.e.., circular versus square - curtains around the maze versus no curtains – see (660)).

Figure 3.Hippocampal Anatomy. A drawing illustrating the local circuitry in the hippocampus, which is referred to as the trisynaptic circuit. Cells in layer two of the entorhinal cortex send projections, via the perforant pathway, to granule neurons in the granule cell layer of the dentate gyrus (DG). Granule neurons project to pyramidal neurons in the CA3 cell layer via the mossy fiber pathway. CA3 pyramidal neurons send projections to CA1 pyramidal neurons via the Shaffer Collaterals. CA1 pyramidal neurons then project back to layer 5 of the entorhinal cortex (EC). Each neuronal population uses an excitatory synaptic connection to stimulate post synaptic neurons in the circuit. Thus, the flow of information arising from the EC is sent to the DG, then the CA3, which sends it to CA1 neurons and then back to the EC.

Figure 4. Androgen and Estrogen Receptor Distribution in the Hippocampus. Both ERα and ERβ are found in CA1, CA3, and the DG of the adult male and female rodent hippocampus. The androgen (AR) is expressed in CA1 and CA3, but not in the DG of adult male and female rodents.

Figure 5. Estrogen Receptor (ER) Signaling. Estradiol can bind to the membrane receptor GPER or can crosses into the cell and binds with cytoplasmic or nuclear ERs of which there are two isoforms (ER α or β). Once bound, ERα or β undergoes a conformational change and dimerizes with another bound ER (forming hetero- or homo-dimers). The complex is transported into the nucleus and binds with and estrogen response elements (ERE) to initiate transcription of estrogen responsive genes or directly interacts with a transcription factor (TF) such as AP-1 to initiate transcription of estrogen responsive genes. Once the mRNA is produced, the message is exported back to the soma and the protein is assembled. Adding to the complexity of signaling, coregulators either coactivators or corepressors interact with the bound ER to alter gene expression. Bound G-protein coupled estrogen receptor (GPER) activates a second

messenger cascade and increases the activity of several kinases, which in turn activate transcription factors to initiate transcription.

Figure 6. Synthesis pathway for both androgens (testosterone and dihydrotestosterone) and estradiol from a precursor cholesterol molecule. Dihydrotestosterone is formed from testosterone via the enzyme, 5α-reductase, whereas estradiol is formed from testosterone via the enzyme, aromatase. Importantly, dihydrotestosterone cannot be converted to estradiol, and vice versa, thus, dihydrotestosterone acts via the androgen receptor, whereas estradiol acts via the estrogen receptor (α, β, or g-protein coupled estrogen receptor). In order to determine if testosterone is acting via either one these receptors, it is customary to use the metabolites to make this determination (Figure adapted from (214) with permission).

Figure 7. Classic Genomic Response of the Androgen Receptor. Testosterone crosses into the soma of the cell and binds with and androgen receptor. Once bound, the androgen receptor undergoes a conformational change and dimerizes with another bound androgen receptor. The complex is transported into the nucleus and binds with and androgen response element (ARE) to initiate transcription of androgen responsive genes. Once the mRNA is produced, the message is exported back to the soma and the protein is assembled.

Cross-References

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Figure 1

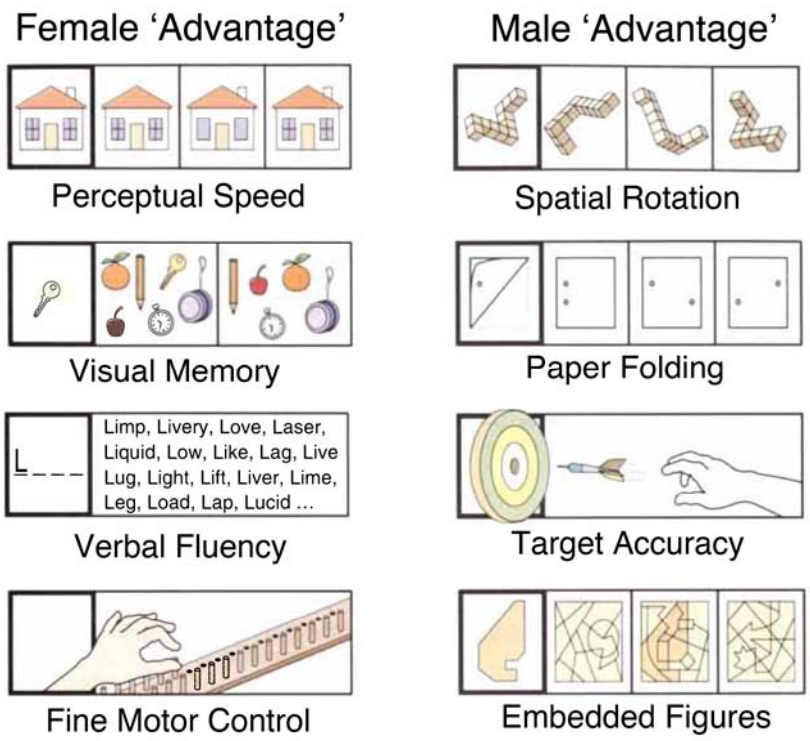
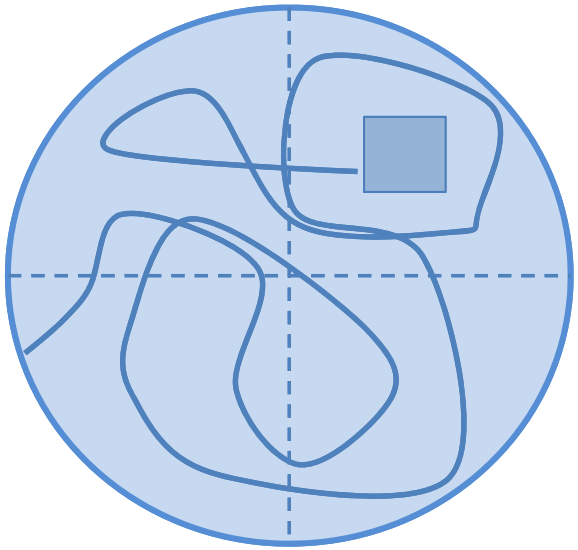
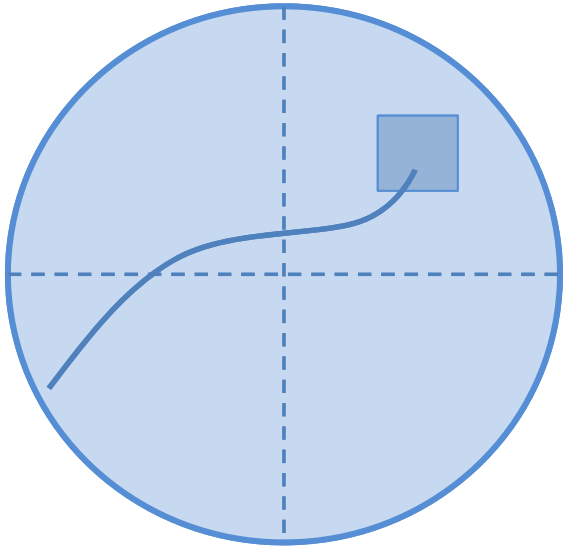

Female 'Advantage'
Male 'Advantage'
Perceptual Speed
Spatial Rotation
Visual Memory
Paper Folding
L _ _ _
Limp, Livery, Love, Laser, Liquid, Low, Like, Lag, Live Lug, Light, Lift, Liver, Lime, Leg, Load, Lap, Lucid ...
Verbal Fluency
Target Accuracy
Fine Motor Control
Embedded Figures

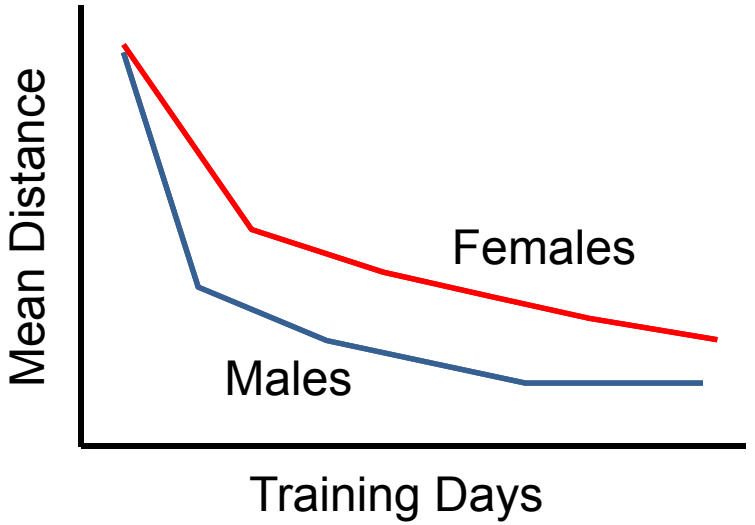
Figure 2



Early Trials



Later Trials



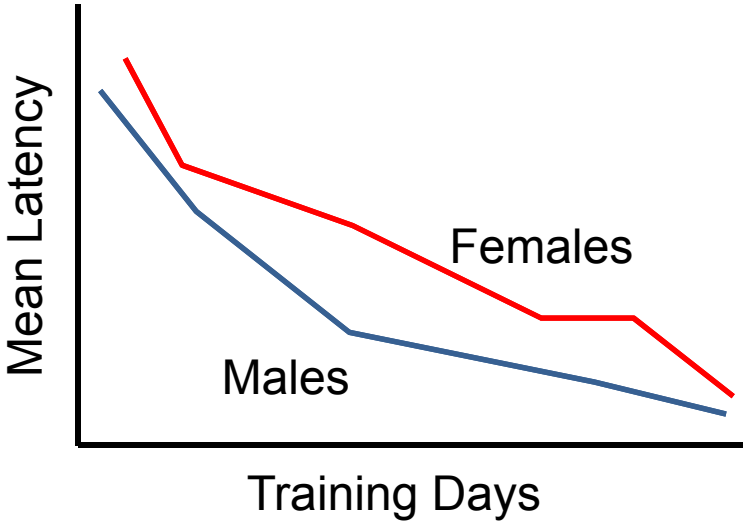
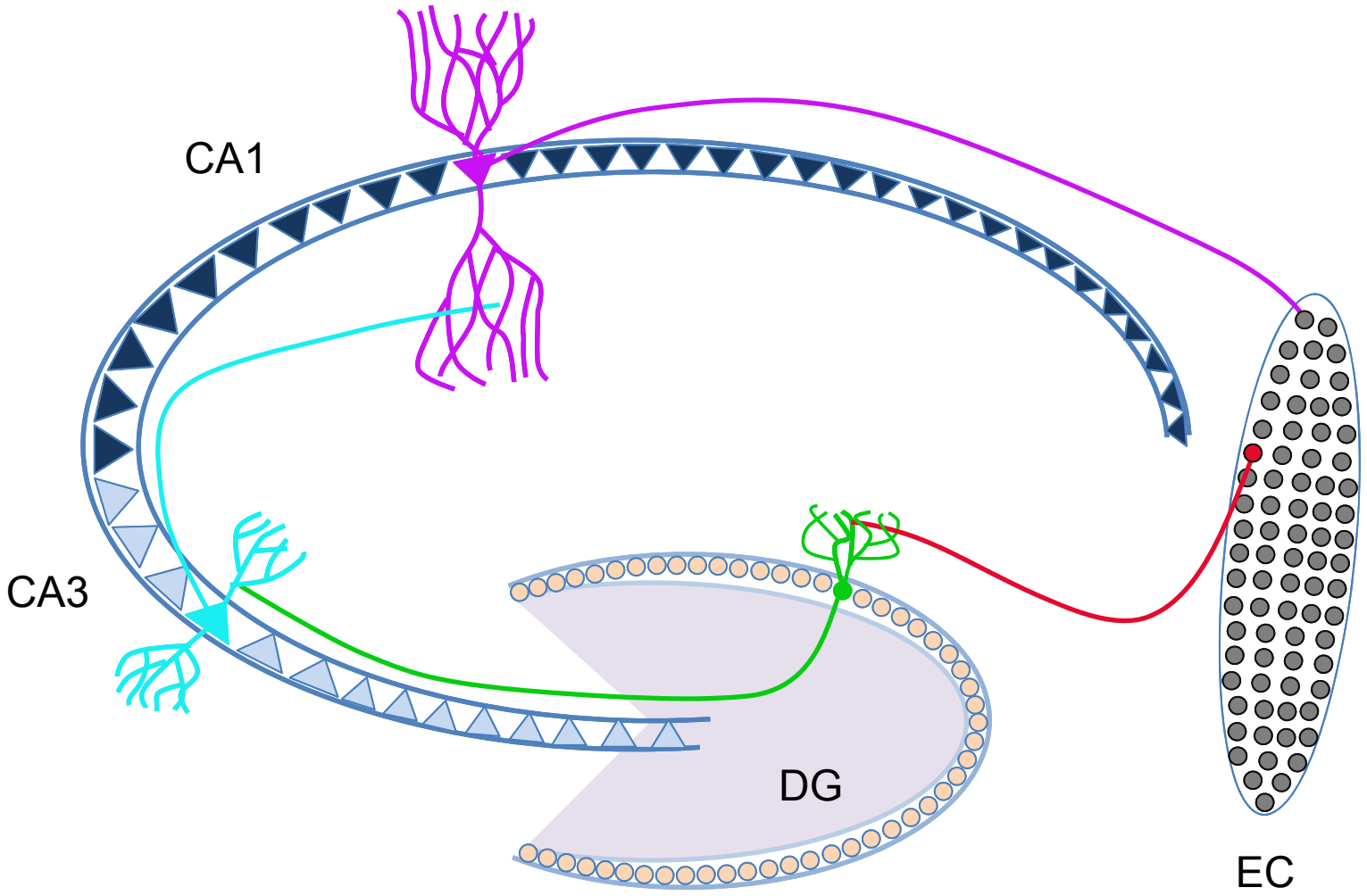


Figure 3

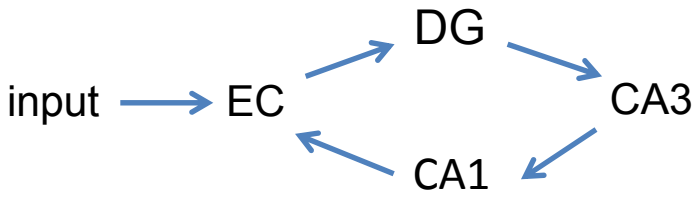


CA1 Pyramidal Neuron

CA3 Pyramidal Neuron

Granule Cell

Entorhinal Cortex Neuron



Information Flow

Figure 4

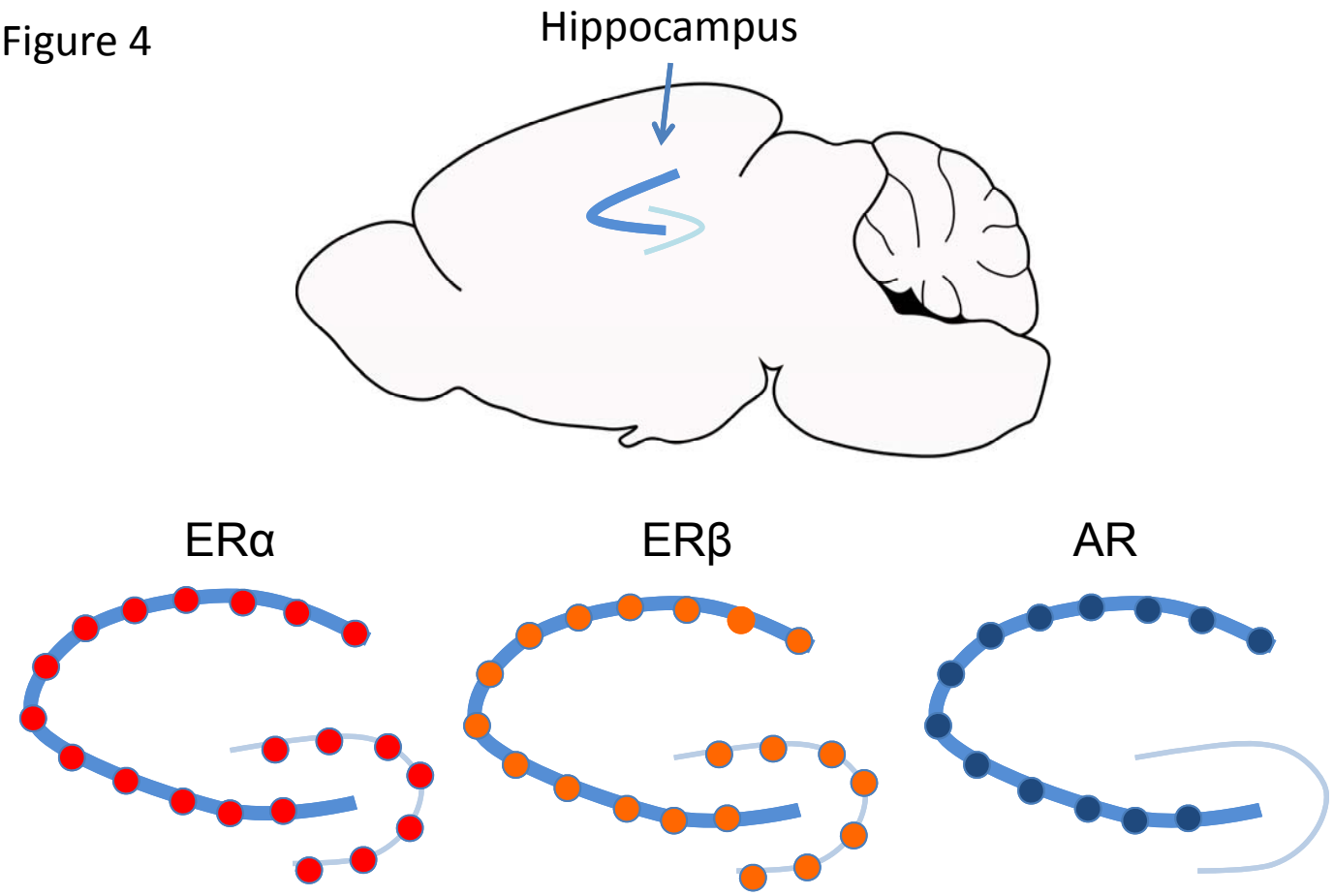
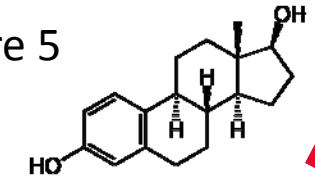


Figure 5



Estradiol

Figure 6.

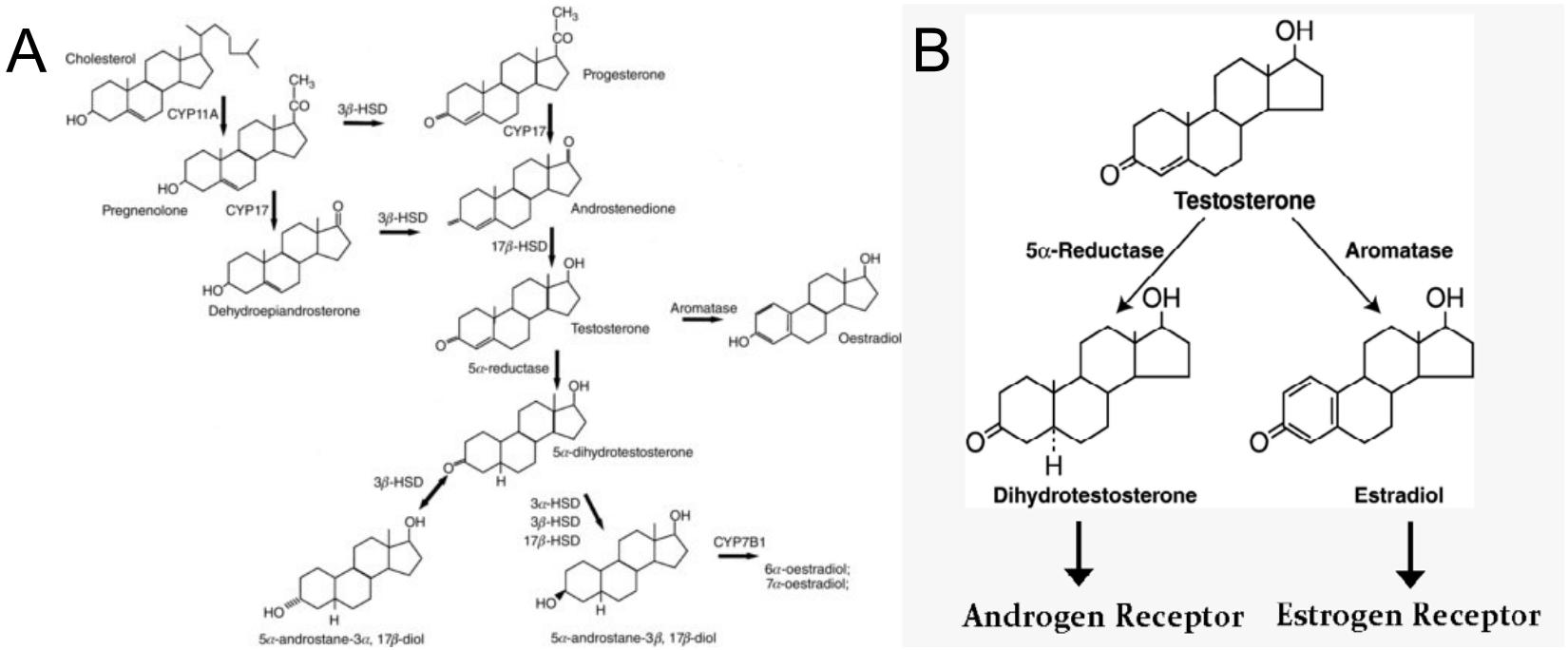
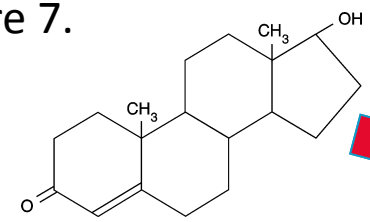
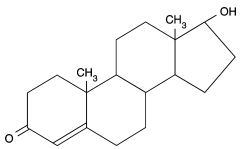

A
Cholesterol
CYP11A
Pregnenolone
3β-HSD
Progesterone
CYP17
Dehydroepiandrosterone
3β-HSD
Androstenedione
17β-HSD
Testosterone
Aromatase
Oestradiol
5α-reductase
5α-dihydrotestosterone
3β-HSD
3α-HSD
3β-HSD
17β-HSD
CYP7B1
6α-oestradiol;
7α-oestradiol;
5α-androstane-3α, 17β-diol
5α-androstane-3β, 17β-diol
B
Testosterone
5α-Reductase
Aromatase
Dihydrotestosterone
Estradiol
Androgen Receptor
Estrogen Receptor

Figure 7.

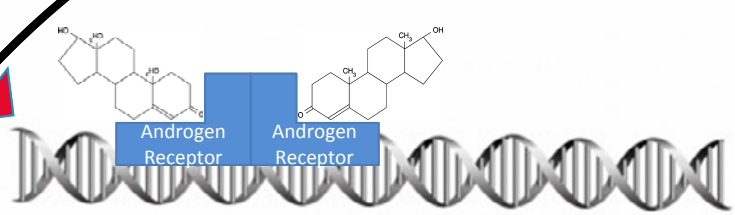


Testosterone



Androgen Receptor

Androgen Receptor | Androgen Receptor



ARE → Transcription

mRNA

Protein