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Module 1, Video 2: Sex differences in hippocampal structural and synaptic plasticity: implications for normal learning and memory

Learning and memory are important cognitive functions with wide-ranging implications for survival. Sex differences in learning and memory are widely reported across species and in humans [1] and vary in their intensity based on the type of memory being studied, with some tasks favoring males and others favoring females. There are also sex differences in plasticity in brain regions critical to learning and memory. This plasticity occurs across the lifespan, leading to critical structural and functional differences that may explain sexual dimorphisms in learning and memory. In this video, we will focus on sex differences in hippocampal structural and synaptic plasticity, with particular attention to how biological sex influences neurogenesis, dendritic morphology, and long-term potentiation (or LTP). We focus on the hippocampus due to its highly plastic nature, abundance of sex hormone receptors, and implication in numerous forms of normal and impaired learning and memory.

Sex differences in hippocampal structural plasticity

Human studies of sex differences in hippocampal volume have shown mixed results, with observed differences likely dependent upon factors like age and pubertal status [2, 3] even after correcting for total brain size. But there are some volumetric differences in hippocampal subregions and the connectivity between them, which may account for functional sex differences in learning and memory [4, 5].

Work in animals also shows region-specific sex differences in hippocampal volume, including the dentate gyrus, CA1 and CA3 [6]. Many of the observed differences reflect morphological differences in the granule neurons and pyramidal neurons that make up the hippocampus [7-9], including the number of dendritic intersections in the dentate gyrus [9], the number of basal dendritic branch points [10] and the number of primary dendrites [11] and dendritic spines [7] in the CA3, and the apical dendritic spine density in the CA1 [12]. Many of these differences also show estrous cycle-dependent structural plasticity.

One sex-dependent variation in hippocampal structural plasticity is observed with dendritic spines. Dendritic spines are small, membranous protrusions from the dendrites of neurons. In mammals, they are the primary site for excitatory synaptic inputs.

Dendritic spine structural plasticity is related to changes in synaptic efficacy, learning and memory, and other cognitive processes. But it is unclear whether dendritic spine

plasticity precedes or is a consequence of behavioral changes, or both. Males and females show basal differences in spine density in the hippocampus, particularly in the CA1 region [8, 13]. Spine density can also fluctuate with the estrous cycle. Over the 4-5 d estrous cycle of the rat, spine density can change as much as 30%. It is the highest during proestrus when ovarian hormones are the highest, and then decreases back down to its lowest point during the estrus phase [14].

The magnitude and appearance of sex differences in other measures of hippocampal dendritic morphology also vary with the estrous cycle.

In addition to basal differences in hippocampal spine density, further sex differences are also observed after sex hormone manipulations [6]. In female rats, fluctuations in endogenous estradiol or the administration of exogenous estradiol increases dendritic spine density in CA1 pyramidal neurons [8, 12, 14]. Ovariectomy decreases spine density to levels that are similar to those of males, particularly in the CA1. This effect is rapidly reversed with estradiol or progesterone treatment in as little as 40 min [8, 12, 15, 16]. Changes in spine density also appear to have functional implications as estradiol-induced increases in CA1 spines also improves learning [17]. However, these effects may not be consistent across species or might be altered when assessed in conjunction with stress or learning paradigms [18].

Dendritic spine density in the CA1 region also fluctuates with sex hormones in males. These changes are driven by testosterone, not the conversion of testosterone to estradiol [19]. Gonadectomy also significantly reduces CA1 dendritic spine density in males, an effect that is reversed by add back therapy of testosterone or dihydrotestosterone, but not estradiol [20, 21]. Therefore, both estradiol and testosterone can regulate spine density.

Sex differences in sex hormone receptor localization

Hippocampal neuronal structural plasticity—including changes in spine density—is evident across the hormone cycle. Much of the research on the mechanisms driving this structural plasticity has focused on estrogen's ability to modify the structure of neurons. The various estradiol receptors are found throughout the hippocampus of both males and females [22] but their subcellular distribution varies across sexes. For example, GPER1 shows similar distribution in males and females, including in the axon, dendritic tree, spine shaft, and terminal endings. As estrogen levels increase, however, increased axonal labeling of GPER1 is found in females [23]. ERα and ERβ, in contrast, exhibit more notable sex differences in their localization with ERα primarily located in dendritic spine heads and the base of the spine shafts in CA1 and CA3 and ERβ localized in the cell body

and dendrite membranes [24]. Sex differences in the subcellular localization of hormone receptors suggest a potential mechanism for how sex hormones lead to hippocampal structural plasticity of males and females as well as across the estrous cycle.

Sex differences in synaptic plasticity

Differences in structural plasticity between males and females can also lead to functional differences in the hippocampus. The most studied form of functional synaptic plasticity is LTP, a cellular correlate for learning and memory [26] that has been studied in the contexts of normal aging, stress-induced pathology, and neurodegenerative diseases [27]. In LTP, high-frequency stimulation applied to the Schaffer collaterals of CA3 neurons leads to changes in the EPSP amplitude of CA1 neurons. LTP has two phases: early LTP, which occurs faster and is mediated by NMDA channels, and late LTP, which requires protein synthesis.

Males exhibit larger early and late LTP compared to females in the dentate gyrus, CA3 and CA1 [28-31]. In females, estradiol enhances the magnitude of NMDA-mediated LTP of CA3-CA1 synapses (reviewed in [32, 33]). There are also variations among females across the estrous cycle. For example, the magnitude of perforant path early-LTP is greater in proestrus compared to diestrus [34].

Some of the observed sex differences in hippocampal LTP can be directly attributed to the variations in sex hormone receptor localization within hippocampal neurons [35, 36]. Thus, it is important to remember that sex differences in structural plasticity should be considered when studying the genomic, cellular and structural bases of hippocampal function.

Sex differences in hippocampal neurogenesis

Neurogenesis refers to the process by which new neurons are generated and integrated into the central nervous system. The hippocampus—and specifically the dentate gyrus—is one of only two sites in the adult mammalian brain that is capable of neurogenesis [38]. As new neurons are integrated into the existing neural circuitry, they have functional impacts under both normal and disease states. Adult hippocampal neurogenesis is also thought to play a major role in the pathophysiology of numerous neurological and psychiatric disorders. Adult neurogenesis is typically studied as changes in neuronal proliferation, migration, differentiation and survival; here we will focus on sex differences in proliferation and survival.

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For proliferation, season- and estrous cycle stage-specific differences have been observed, with greater proliferation in the dentate gyrus of females versus males during the non-breeding season or during proestrus compared to both non-proestrus females and males [40]. These differences may be species specific, as studies show effects in voles and rats, but not in mice [41, 42].

In contrast to cell proliferation, the basal survival of new neurons does not seem to differ between males and females across species [39-41, 43]. When basal differences in survival do occur, it is usually in the ventral dentate gyrus, with greater levels in males [44]. Similarly, endogenous sex hormones such as androgens and estrogens can modulate adult hippocampal cell survival differentially between males and females [45-47]. Changes in aspects of adult neurogenesis are also observed after a variety of experimental and environmental exposures, and these effects also show sex differences. Most notably, stress and the exposure to hippocampus-dependent learning tasks can also differentially regulate the survival of new hippocampal cells in male and female rodents, with learning effects dependent on the type of task, the quality of learning, and/or task difficulty. For example, males outperform females in acquiring the spatial version of the Morris water maze [48], which was associated with enhanced neuronal survival in the dentate gyrus; a similar association was also found in the trace eyeblink conditioning task during diestrus [44].

Sex differences in learning and memory

The vast majority of studies examining sex differences in hippocampal-dependent learning and memory have used young post-pubertal rodents that are gonadally intact. While a full review of all sex differences in learning and memory is beyond the scope of this video, we do focus on two well-studied types of hippocampal memory. The first is spatial memory. Spatial memory is primarily assessed with the Morris water maze or radial arm maze tasks, both of which have been adapted into virtual computerized versions for use in humans, allowing for improved translation of these findings.

Two separate meta-analyses, one in humans [50] and one in rodents [51], concluded that spatial memory performance favors males in young adults and rodents. However, many factors, including stress associated with the task, the type of task, the testing protocol, and age of the animals may influence the findings, making replication of sex differences across paradigms and laboratories difficult [51].

The second type of hippocampal-dependent memory is object memory. Most of the available evidence suggests that females outperform males in tests of object memory. These tests involve presenting an animal with two identical objects during a training

phase and then switching out one of those objects during a test phase [52]; animals should spend more time with the novel object versus the familiar object. Object memory tasks show high sensitivity to sex steroids in adulthood, and females perform better when estrogen and progesterone levels are elevated during the estrous cycle [53]. Fewer studies have been performed in males, but intrahippocampal infusion of estradiol post-training seems to enhance object memory in gonadally intact male mice [54]. These data suggest that both spatial and object memory performance may be directly related to circulating steroid hormone levels in both males and females.

The role of estrogens in hippocampal-dependent learning and memory

Learning and memory involves a series of processes that include the encoding, storage and retrieval of information.

A causal link between changes in dendritic spine density and alterations in learning and memory has not been definitively proven. However, because estrogens rapidly increase synaptic density both in vivo [16] and in vitro [55, 56], as well as enhance learning and memory within the same time frame (e.g., [57-65]), it is reasonable to assume these processes work together. A two-step process for estrogen's effects on learning and memory has been proposed. In Step 1, estrogens may prime neurons to form lasting connections by first creating silent synapses and increasing dendritic spine density. This likely occurs through actin cytoskeleton dynamics [66] and de novo protein synthesis [67-70]. In Step 2, stimulation leads these neurons to undergo LTP. In this process, novel mature synapses are only formed when dictated by neuronal activity. While this effect was investigated in cultured embryonic cortical neurons, this "two-step wiring plasticity" process may also explain the enhancing effect of estrogen on learning in other brain regions, such as the hippocampus. However, because other potential mechanisms exist that may not involve dendritic spine changes [71], further studies are needed.

Structural and synaptic plasticity within the hippocampus allows for changes and adaptability that facilitate many necessary processes, such as learning and memory. It also makes the hippocampus susceptible to disease. A variety of factors can influence the effects of estrogens on hippocampal plasticity, including sex, age, dose, and hormonal state. Understanding how sex hormones interact with these factors in healthy brains is essential for understanding the biological bases of dysregulation of these processes and various disease states. The marked sex differences in the prevalence of many disorders related to dysregulated hippocampal function highlight the importance of considering sex as a biological variable in preclinical research.

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