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Review article

Regulation of object recognition and object placement by ovarian sex steroid hormones

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HIGHLIGHTS

- 17β-Estradiol (E_2) and progesterone (P_4) potently regulate hippocampal memory.
- Object recognition (OR) and object placement (OP) are enhanced by E_2 and P_4.
- E_2 and P_4 rapidly activate the molecular processes underlying object memory.
- Both endogenous and exogenous E_2 and P_4 affect object memory across the lifespan.
- This review discusses regulation of object memory by E_2 and P_4 in female rodents.

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ABSTRACT

The ovarian hormones 17β-estradiol (E_2) and progesterone (P_4) are potent modulators of hippocampal memory formation. Both hormones have been demonstrated to enhance hippocampal memory by regulating the cellular and molecular mechanisms thought to underlie memory formation. Behavioral neuroendocrinologists have increasingly used the object recognition and object placement (object location) tasks to investigate the role of E_2 and P_4 in regulating hippocampal memory formation in rodents. These one-trial learning tasks are ideal for studying acute effects of hormone treatments on different phases of memory because they can be administered during acquisition (pre-training), consolidation (post-training), or retrieval (pre-testing). This review synthesizes the rodent literature testing the effects of E_2 and P_4 on object recognition (OR) and object placement (OP), and the molecular mechanisms in the hippocampus supporting memory formation in these tasks. Some general trends emerge from the data. Among gonadally intact females, object memory tends to be best when E_2 and P_4 levels are elevated during the estrous cycle, pregnancy, and in middle age. In ovariectomized females, E_2 given before or immediately after testing generally enhances OR and OP in young and middle-aged rats and mice, although effects are mixed in aged rodents. Effects of E_2 treatment on OR and OP memory consolidation can be mediated by both classical estrogen receptors (ERα and ERβ), and depend on glutamate receptors (NMDA, mGluR1) and activation of numerous cell signaling cascades (e.g., ERK, PI3K/Akt, mTOR) and epigenetic processes (e.g., histone acetylation, DNA methylation). Acute P_4 treatment given immediately after training also enhances OR and OP in young and middle-aged ovariectomized females by activating similar cell signaling pathways as E_2 (e.g., ERK, mTOR). The few studies that have administered both hormones in combination suggest that treatment can enhance OR and OP, but that effects are highly dependent on factors such as dose and timing of administration. In addition to providing more detail on these general conclusions, this review will discuss directions for future avenues of research into the hormonal regulation of object memory.

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Contents

1. Introduction

The object recognition (OR) task was first introduced in 1988 to provide a method of testing episodic memory in rodents that was similar to methods used in clinical neuropsychology [1]. The task capitalizes on rodent's inherent predilection for novelty. In the most common version of the task, rodents explore two identical objects during a single training session. During the single test session, subjects are then allowed to explore an object identical to the training objects and a novel object. More time spent exploring the novel object indicates memory for the familiar object. In the years since its introduction, OR has become prevalent in rodent learning and memory studies, where it is used alone or as part of a test battery to investigate the effects of lesion, genetic, or pharmacological manipulations. The task has also evolved to assess spatial memory in rodents via a modified version referred to as object placement or object location (referred to herein as object placement) [2]. As such, OR is used to assess memory for the identity of objects (i.e., "what") and object placement (OP) is used to assess memory for the location of objects (i.e., "where"). To this end, OR in rodents is generally considered a non-spatial memory task involving the hippocampus, perirhinal, entorhinal, and parahippocampal cortices [3–5], whereas OP in rodents is considered a spatial memory task that relies primarily on the hippocampus [6]. However, the brain regions involved in OR in rodents and other species have been the subject of intense debate, particularly the role of the hippocampus in mediating OR. Although this issue is not the primary focus of this review, rodent data from our laboratory and others do support a role for the hippocampus in OR, as will be discussed below. Therefore, this review is written from the perspective that the hippocampus is essential for memory formation in both OR and OP. Because the amount of data collected on hormonal regulation of object memory in rodents far outnumbers the amount of data collected in other species, this review will limit discussion to studies employing rats or mice as subjects.

OR and OP are particularly well suited for investigating the molecular processes underlying the formation of hippocampal-dependent memories in rodents. First, they take advantage of a rodent's natural tendency to explore novel stimuli, while avoiding other potentially confounding variables. For example, no rule learning is required, nor are any rewarding or punishing stimuli involved that may influence motivational, rather than mnemonic, aspects of task performance [1,7]. Therefore, memory can be measured in the absence of confounds due to the stress of nutrient restriction (as commonly used in the radial arm maze and T-maze), shock (as used in fear conditioning), or submersion in water (as used in the Morris water maze). Second, OR and OP are true one-trial learning tasks. This quality makes them ideal for studying the effects of acute drug or hormone treatments, which may be given pre- or post-training to investigate effects on different phases of learning and memory such as encoding, consolidation, and retrieval.

This unique combination of one-trial learning in a relatively stress-free environment has appealed in recent years to behavioral neuroendocrinologists seeking to identify the molecular mechanisms through which sex steroid hormones, such as 17β-estradiol (E_2) and progesterone (P_4), influence memory across the rodent lifespan. The low stress associated with OR and OP testing is advantageous for behavioral endocrinologists because corticosteroids released in response to more stressful tasks may interact with ovarian hormones and could confound the interpretation of results [8,9]. Tasks like OR and OP that do not provoke a strong stress response allow for effects of ovarian hormones on memory to be more clearly identified in rodents. Furthermore, behavioral endocrinologists have found that E_2 and P_4 can very rapidly impact hippocampal function [10–13], and therefore, the one-trial nature of OR and OP makes these tasks particularly useful for identifying the molecular mechanisms underlying hormonal regulation of memory consolidation. As such, both OR and OP have been widely used in the past decade to study the effects of sex steroid hormones on hippocampal learning and memory in rats and mice.

However, as will be seen below, investigators have taken very different approaches to studying hormonal regulation of object memory in rodents. Both rats and mice of various strains have been used, with studies employing mice generally outnumbering those using rats. Although species differences could influence the effects of hormones on OR, OR does not appear to differ between

male rats and mice [14], and effects of E_2 and P_4 on OR and OP are remarkably consistent among rat and mouse studies. However, an interesting new report showing that the effects of estrogen receptor agonists on OR differ in two mouse strains suggests that strain or species may influence the receptor mechanisms through which hormones regulate object memory [15]. It is also important to note that although several studies have used gonadally intact females, the vast majority of studies to date administered exogenous hormones to ovariectomized females because removal of the ovaries eliminates the ovarian hormone fluctuations generated by the estrous cycle. In most studies, treatment was started at the time of ovariectomy or within a week afterward, but recent data show that long periods of ovarian hormone deprivation after ovariectomy eliminate the memory-enhancing effects of E_2 on OR [16]. As such, timing of treatment relative to ovariectomy is an important variable for investigators to consider. Among exogenous hormone studies, most administered only E_2. Therefore, much less is known about the effects of P_4 on memory, alone or in combination with E_2. Finally, a key difference among many studies is the timing of treatment relative to testing, as an increasing number of studies have administered E_2 and P_4 immediately *after* training to examine rapid effects of these hormones on object memory consolidation. In general, E_2 or P_4 given prior to, or immediately after, training enhance OR and OP, so the neural mechanisms underlying these effects are likely to be similar. As with any drug treatment, however, the effects of these hormones on object memory depend on many factors such as dose, route of administration, and age of subjects. Nevertheless, E_2 and P_4 generally enhance memory in the OR and OP tasks, as will be illustrated in the sections below.

The primary goal of this review is to survey literature examining the regulation of OR and OP in rats and mice by ovarian sex steroid hormones. To set the stage for this discussion, we will first address the role of the hippocampus in OR, provide an overview of ovarian hormone regulation of hippocampal function, and detail the protocols most commonly used in hormone studies. We will then describe the effects of natural estrous cycling and exogenous hormone administration on OR and OP. Finally, we will end by reviewing the molecular mechanisms known to mediate the memory-enhancing effects of E_2 and P_4 on OR and OP, and discuss how the reduction of ovarian hormone levels during aging affects memory in these tasks. Our intent is to highlight the importance of ovarian sex steroid hormones in regulating object memories in rodents and encourage investigators to consider the role that these hormones may play in their own experimental designs.

2. Role of the hippocampus in object recognition

Since their introduction in the 1980s and 1990s, one-trial OR and OP tasks have gained traction as standard tests for rodent memory in behavioral neuroscience and behavioral neuroendocrinology alike. Sensitive to hormones, aging, and drug treatments, OR and OP are most commonly associated with measures of episodic hippocampal memory. In addition to its role in other well known tasks such as the Morris water maze [17], contextual fear conditioning [18], and radial arm maze [18], the hippocampus also plays a pivotal role in OR and OP [12,19–21]. Several researchers have conducted systems-level investigations to determine which brain regions are involved in mediating the non-spatial and spatial memory components of these tasks. For example, the hippocampus, cingulate cortex, and fornix have been implicated in modulating OP memory [2]. Although there is little debate regarding the role of the hippocampus in mediating spatial memory [6,22,23], the role of the hippocampus in OR remains controversial [4,23–29] and may depend on the extent to which spatial information is available. Despite compelling evidence implicating the entorhinal and perirhinal cortices in mediating OR memory [5,24,30], considerable data also suggest an important role of the hippocampus in recognition memory in rodents, non-human primates, and humans [19–21,31,32]. The bulk of this evidence comes from inactivation studies demonstrating OR memory impairment when the hippocampus is lesioned or inactivated [3,6,19,21,33]. Importantly, impairments are not observed when lesions are made to the fornix or cortical regions adjacent to the hippocampus, suggesting a specific role for the hippocampus in OR memory [19]. Although some studies suggest that a substantial lesion or pharmacological inactivation of greater than 50% of the total hippocampal volume is required [6], a recent study demonstrated significant OR impairment in mice when only about 1% of the dorsal hippocampus was inactivated [21]. This striking finding suggests that even the smallest disruption to dorsal hippocampal circuitry can significantly disrupt OR memory.

Object recognition memory is also disrupted when specific receptors or cell-signaling pathways are inhibited in the hippocampus. For example, pharmacological inactivation of the dorsal hippocampus by $GABA_A$ agonists, NMDA antagonists, or inhibitors of ERK/MAPK cell signaling, histone acetylation, and protein synthesis significantly impair OR memory in rats and mice [10,20,21,34,35]. Other studies report molecular and physiological alterations in the hippocampus resulting from OR training, including changes in synaptic physiology, neurotransmitter release, and activation of immediate early genes [21,36,37]. For example, long-term potentiation (LTP)-like changes occur in hippocampal CA3-CA1 during the consolidation period following OR training [36]. Moreover, mice do not demonstrate intact memory for the familiar object if these LTP-like changes are disrupted prior to presentation of the objects [36], suggesting that the hippocampus plays an essential role in OR memory consolidation. The presentation of a novel object during the testing phase facilitates the firing of CA1 neurons in the dorsal hippocampus and increases excitatory glutamate release [21]. Because these events occur only in the presence of a novel object, and not upon re-exposure to two familiar objects [21], this finding suggests that the dorsal hippocampus is activated by novelty and plays a role in novelty detection in the OR task. Further support for a role of the hippocampus in OR is provided by a study demonstrating significantly more *c-fos* expression in the dentate gyrus of rats tested in OR than in the dentate of home cage control rats [37]. This immediate early gene expression suggests engagement of the hippocampus during OR training and/or testing. Collectively, these data support the involvement of the hippocampus in OR, and highlight the carefully orchestrated molecular processes required in this region for the successful formation and storage of recognition memories in the rodent brain.

3. Effects of ovarian hormones in the hippocampus: A general overview

Although the contributions of the hippocampus to OR may be the subject of continued debate, an increasing body of research supports a role for the hippocampus in mediating OR memory consolidation. As a result, OR has become a useful tool for studying the effects of various neuromodulators, including sex steroid hormones, on hippocampal memory. To provide context for a discussion of this work, this section will describe the ways in which ovarian sex steroid hormones regulate hippocampal function. For more detail on this subject than can be provided here, we recommend several recent reviews [38–42].

3.1. Early development

Sex steroid hormones regulate brain function throughout the lifespan. These hormones play an integral organizational role in

the sexual differentiation of the brain during the prenatal and early postnatal periods in both males and females [43–50]. Although early studies focused largely on brain regions related to sexual behavior, such as the hypothalamus and preoptic area, more recent findings demonstrate that sex steroid hormones also promote sexual differentiation of the hippocampus, basal forebrain, and cerebral cortex [51,52]. Such differentiation can have long-term consequences for memory function later in life, as suggested by findings in rats indicating that neonatal hormone exposure contributes to a male advantage in hippocampal-dependent spatial memory in adulthood [53]. Indeed, this sex difference in adulthood can be reversed by gonadectomy in males and E_2 treatment in females before postnatal day 10 [53], suggesting that early hormonal exposure shapes the hippocampus into a "male" or "female" pattern. However, it should be noted that the magnitude of sex differences in the hippocampus is considerably smaller than those associated with reproductive brain regions and behaviors [53,54].

3.2. Hippocampal morphology

In addition to their effects on brain organization, sex steroid hormones exert activational effects on the brain throughout adulthood. In female mammals, estrogens and progestins are made primarily in the ovaries, although these hormones are also synthesized in other organs including the brain. In fact, levels of E_2 are higher in the hippocampus than in serum in both male and female rats [55,56]. Serum levels of estrogens and progestins fluctuate substantially in response to the release of hormones from the hypothalamus and anterior pituitary. The rodent hormone cycle, called the estrous cycle, lasts 4–5 days and is divided into four phases (proestrus, estrus, metestrus, and diestrus) that each last about 24 h [57]. The cycle is characterized by peaks of E_2 and P_4 just prior to ovulation during the proestrus phase. Levels of both hormones drop steeply after ovulation and are, therefore, quite low during the subsequent estrus phase of the cycle. The earliest work to demonstrate that the adult hippocampus is sensitive to ovarian hormones examined how dendritic spine density in the CA1 region of the hippocampus was affected by hormonal fluctuations during the estrous cycle or exogenous administration of E_2 and P_4. This work, published in the early 1990s by Bruce McEwen and colleagues, showed that dendritic spine density was 30% higher during proestrus than estrus [58]. Furthermore, bilateral removal of the ovaries significantly decreased spine synapse density relative to intact females, an effect that could be reversed within hours by acute E_2 treatment alone or E_2 plus P_4 [59]. In addition to dramatic changes in spine number, spine synapses were also increased during proestrus [60] and by exogenous E_2 treatment [61]. Interestingly, P_4 had a biphasic effect on spine synapses, initially increasing CA1 spine density during the first 2–6 h after injection, but then sharply decreasing spine density afterward [61]. In the years since, these findings have been replicated and expanded upon by numerous labs [62–69]. Collectively, these landmark findings provided the first evidence demonstrating that ovarian hormones could modify the CA1 synaptic morphology thought to support the formation of lasting memories.

3.3. Neural mechanisms through which estradiol affects hippocampal function

Numerous subsequent studies have expanded upon these seminal discoveries, demonstrating E_2's role as a potent regulator of cellular events in the hippocampus critical for synaptic plasticity and memory. Systemic, intracranial, or in vitro applications of E_2 increase hippocampal expression of synaptic proteins such as synaptophysin, spinophilin, syntaxin, and postsynaptic density-95 [70–72], increase intrinsic excitability [42], facilitate hippocampal LTP [73], and promote neurogenesis in the dentate gyrus [74]. Some of these effects may be due to the binding of E_2 to its canonical intracellular receptors, ERα and ERβ. ERα and ERβ are found in dendritic spines, dendrites, axon terminals, and the nuclei of hippocampal pyramidal neurons [33,75,76]. Hippocampal ERα is also present within cholinergic axons and terminals [77], and in the cytoplasm and nucleus of GABAergic interneurons, where it facilitates an E_2-induced decrease in GABAergic tone that promotes pyramidal neuron spinogenesis [78]. The classical mechanism of estrogen action involves the formation of an E_2-ER complex in the cytoplasm, the translocation of the complex into the nucleus, and the binding of the complex to an estrogen response element (ERE) on the DNA to initiate gene transcription. However, E_2 can also influence neuronal function by rapidly activating cell-signaling cascades like extracellular signal-regulated kinase (ERK) and phosphatidylinositol 3-kinase (PI3K) [10,12,79–81], induce post-translational epigenetic modifications such as histone acetylation and DNA methylation [35,79], and initiate mammalian target of rapamycin (mTOR)-mediated protein synthesis [34]. The classical ERE-mediated mechanism is too slow to account for these effects, which can occur within five minutes of dorsal hippocampal E_2 infusion [10,34]. It is now well accepted that E_2 can rapidly influence hippocampal function via interactions between ERs and neurotransmitter receptors (e.g., mGluRs, NMDA receptors) and/or by binding to novel ERs in the plasma membrane (e.g., GPER/GPR30, Gq-mER) [12,80,82]. Studies of ER localization in the hippocampus support the notion that canonical ERs are positioned within spines and axon terminals for rapid local modulation of hippocampal function [83]. For example, our own laboratory has demonstrated that rapid activation of hippocampal cell signaling, epigenetic processes, and mTOR-mediated protein synthesis is necessary for OR memory consolidation [10,12,34,35] (see Section 7 below). Collectively, these studies demonstrate that E_2 can influence hippocampal function in numerous ways to regulate hippocampal memory formation.

3.4. Neural mechanisms through which progesterone affects hippocampal function

Much less is known about the neural mechanisms through which P_4 regulates hippocampal function and memory formation. However, like E_2, P_4 can also enhance hippocampal LTP [84], neurogenesis [85,86], ERK signaling, and mTOR-dependent local protein synthesis [87]. Nevertheless, understanding how P_4 influences memory is considerably more challenging than E_2 because P_4 serves as an obligatory precursor for the synthesis of other steroids including estrogens, androgens, and glucocorticoids. Thus, P_4 may influence hippocampal function via conversion to other steroid hormones that subsequently bind to their cognate receptors. Furthermore, P_4 is metabolized into neuroactive steroids like 3α,5α-tetrahydroprogesterone (3α,5α-THP or allopregnanolone) that can bind to the steroid binding site on $GABA_A$ receptors and regulate synaptic excitability [88]. In addition, P_4 shares with E_2 the complexity that it can bind to two types of receptors: canonical intracellular progesterone receptors (PRs), thought to regulate slow transcription-mediated (i.e., classical) events, and plasma membrane-bound receptors (mPRs), thought to mediate rapid cell signaling-initiated (i.e., non-classical) effects. As such, there are at least three ways in which P_4 may affect hippocampal memory: (1) binding to intracellular PRs, which then translocate to the nucleus and initiate gene transcription at a P_4 response element (PRE), (2) binding to mPRs and rapidly activating cell-signaling cascades like ERK and PI3K, and (3) metabolism to E_2, glucocorticoids, or 3α,5α-THP, which can then bind to estrogen receptors (ERs), $GABA_A$ receptors, and glucocorticoid receptors (GRs). Within the hippocampus, intracellular PRs are located within dendritic spines,

dendrites, cell bodies, and axons of principal neurons in CA1, CA3, and the dentate gyrus, as well as in GABAergic interneurons and glia [83,89]. Therefore, like ERs, PRs are positioned to act locally to regulate hippocampal function. Indeed, our laboratory has found that dorsal hippocampal infusion of P_4 in ovariectomized mice activates ERK and mTOR cell signaling in the dorsal hippocampus within five minutes [87]. Interestingly, P_4 has a biphasic effect on p42 ERK activation, at first increasing phospho-p42 ERK levels five minutes after infusion and then decreasing levels 15 min after infusion, before returning to baseline 30 min later [87]. Similarly, systemic P_4 in ovariectomized rats at first increases, and then decreases, CA1 dendritic spine density before levels return to baseline [61]. Such biphasic effects of P_4 on hippocampal function further complicate attempts to understand how P_4 regulates hippocampal memory.

3.5. General effects of estradiol and progesterone on hippocampal memory

In the two decades since the initial demonstration that ovarian hormones regulate CA1 dendritic spine density, hundreds of studies have examined the effects of E_2 and/or P_4 on memory in rodents, non-human primates, and humans. As such, a thorough evaluation of this literature is beyond the scope of this article, and the reader is encouraged to consult any of the numerous reviews on this subject (e.g., [39,90–98]). However, some broad generalizations may be drawn, particularly among rodent studies. In rodents, E_2 is generally thought to facilitate hippocampal memory, although its effects depend on many factors, including age, dose and duration of treatment, duration of hormone loss prior to treatment, method of inducing ovarian dysfunction, timing of treatment relative to testing, type of memory tested, and task difficulty [95,99,100]. The vast majority of studies have examined the effects of exogenously administered E_2 on spatial memory in ovariectomized female rodents. Consistent with the beneficial effects of exogenous E_2 on hippocampal plasticity, spinogenesis, and neurogenesis, exogenous E_2 administered to young ovariectomized rats and mice generally enhances spatial memory in the Morris water maze, radial arm maze, and T-maze [9,99–116]. E_2 also facilitates memory formation in non-spatial tasks, including social recognition [62], inhibitory avoidance [117–119], and trace eyeblink conditioning [120]. In accord with these other tasks that assess hippocampal function, E_2 generally enhances memory consolidation in the OR and OP tasks; these data will be detailed in the sections below.

The effects of P_4 on hippocampal memory differ depending on its administration relative to training and testing. Chronic systemic administration of P_4 prior to training impairs footshock avoidance learning and spatial working memory in young ovariectomized mice and rats [121,122], perhaps due to the anxiolytic and analgesic effects of P_4 metabolites at $GABA_A$ receptors [123–125]. On the other hand, acute administration of P_4 prior to training (systemic) or immediately after training (intrahippocampal) has no effect on spatial memory in the Morris water maze [126,127] or radial arm maze [128] in young ovariectomized rats. These data suggest that P_4 treatment prior to training impairs or has no effect on memory in these behavioral tasks. In contrast, acute systemic or intrahippocampal administration of P_4 immediately *after* training enhances Y-maze inhibitory avoidance and OR in young ovariectomized female rodents [127,129,130], and OR in ovariectomized middle-aged and aged mice [131], suggesting that P_4 can facilitate memory consolidation if present only during the memory consolidation period immediately following learning. It should also be noted that P_4 is often administered in conjunction with E_2 because E_2 levels surge prior to P_4 levels during the natural estrous cycle. In some cases, systemic P_4 administered immediately after training blocks the memory-enhancing effects of E_2 (e.g., on spatial memory in the Morris water maze in aged female mice; [132]) and in other studies, the combination of E_2 and P_4 enhances memory (e.g., on OR in young ovariectomized mice; [133]). In general, combined E_2 and P_4 treatment enhances object memory, but effects are dose dependent. Data on the effects of P_4, alone or in combination with E_2, on OR and OP will be discussed more comprehensively in the sections below.

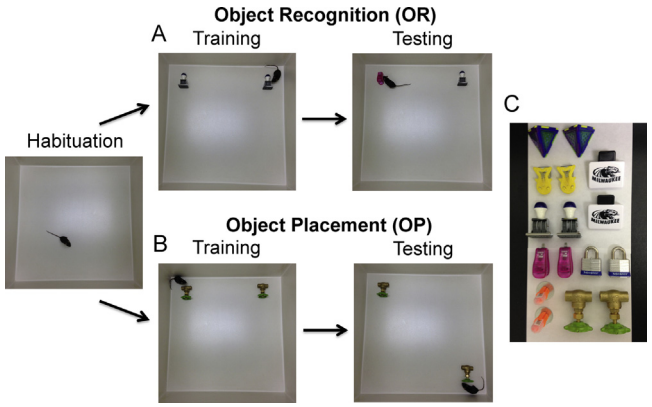

Fig. 1. Overview of the object memory testing protocols discussed in this review. Mice are first habituated to an empty arena prior to beginning behavioral training (habituation). (A) In object recognition (OR), mice are then allowed to explore two identical novel objects placed in the arena (training). Finally, retention is tested by presenting mice with one novel and one familiar object (testing). Mice who remember the familiar object spend more time exploring the novel object relative to the familiar object or to chance. (B) Object placement (OP) uses the same apparatus and general procedure, but during testing, one training object moves to a new location in the arena, rather than being replaced with a new object. (C) Object pairs used in our laboratory's OR and OP protocols.

4. OR and OP protocols typically used in behavioral endocrinology

Since their initial introduction for use in rats, OR and OP have been extended for use in mice and modified in variety of ways to suit the needs of different investigators and their experimental questions [1,134–136]. Modifications include varying the number and size of the objects, size and shape of the testing arena, light levels in the testing arena, duration of habituation, and delay between training and testing. Although the experimental protocols for OR and OP differ somewhat among laboratories, most protocols include three stages: habituation, training (also referred to as a sample phase), and testing (also referred to as a discrimination phase) (Fig. 1). Habituation serves to familiarize the subject to the testing arena and environment. On average, habituation ranges from 5 to 10 min per day for 1–4 days prior to training. During the training or sample phase, two identical objects are presented for exploration, and the time spent exploring each object is recorded. The amount of time allowed for subjects to investigate the objects during training varies by protocol, with most investigators typically using a predetermined limit of 3–20 min. The interval between training and testing can be manipulated to assess the memory-impairing or memory-enhancing effects of experimental manipulations. For example, some experimenters use as little as five minutes, whereas others use up to seven days [63,137–139]. During testing, one of the familiar objects from training is replaced by a novel object (Fig. 1A), and time spent investigating each object is again recorded (other dependent variables include number of visits to the objects and total exploration time). Because rodents tend to explore novelty, they should spend more time exploring the new object if they remember the familiar object. Therefore, recognition memory is considered intact when a subject spends significantly more time exploring the new object than either

Table 1
Effects of endogenous ovarian sex steroid hormones on object recognition and object placement.

Species	Age	Object recognition	Object placement	Ref. no.	Reference
Estrous cycling					
Rat	Young	Proestrus outperformed diestrus and estrus; estrus outperformed diestrus	Not tested	[129]	Walf et al. (2006)
Rat	Young	Memory intact in all phases of the estrous cycle	Memory intact during estrus, but not other stages	[141]	Sutcliffe et al. (2007)
Rat	Young	Not tested	Proestrus and estrus outperformed diestrus	[144]	Frye et al. (2007)
Rat	Young	Proestrus outperformed diestrus	Proestrus outperformed diestrus	[143]	Paris and Frye (2008)
Mouse	Young	Memory intact in wild-type mice in proestrus, but not wild-type or ERβ knockout mice in diestrus	Not tested	[142]	Walf et al. (2009)
Pregnancy					
Rat	Young	Not tested	Rats in 3rd trimester, post-partum, or lactating outperformed rats in 1st trimester	[144]	Frye et al. (2007)
Rat	Young	Pregnant outperformed non-pregnant	Pregnant outperformed non-pregnant	[143]	Paris and Frye (2008)
Estropause					
Rat	Middle-aged	Rats with intact reproductive function outperformed rats with declining reproductive function	Not tested	[210]	Paris et al. (2011)

the familiar object or than chance. Training and testing for OP is identical to OR, except that one of the identical objects from training is moved to a new location in the arena during testing (Fig. 1B). Intact spatial memory is indicated if a subject spends significantly more time with the moved object during the testing phase than either the unmoved object or than chance. When used together, these one-trial tasks provide low stress methods to assess both spatial and non-spatial memory in rodents.

OR and OP data can be analyzed using several different dependent measures. Discrimination ratios are often calculated when investigators do not set a minimum criterion for active exploration time, and instead set a maximum trial time regardless of the amount of active object exploration. Discrimination ratios can be calculated by dividing the time spent exploring the novel or moved object minus the time spent exploring the familiar or unmoved object, by the sum of the total exploration time for both objects ($T_{novel} - T_{familiar}/T_{novel} + T_{familiar}$). This ratio is sometimes multiplied by 100 to obtain a percentage. Regardless, it is essential to divide the difference in exploration time between the two objects by the total exploration time because exploration time will vary among subjects. Chance performance is indicated by ratios near 0, whereas ratios of approximately 0.5 or above indicate a preference for the novel object. Another commonly used discrimination ratio is calculated using the equation ($T_{novel}/(T_{novel} + T_{familiar})$), which can also be multiplied by 100 to obtain a percentage. Values of greater than 0.5 indicate that the subject can successfully discriminate between the two objects. For both discrimination ratio equations, the resulting data are limited in range (e.g., between 0 and 100) and so cannot be truly normally distributed. Therefore, ratio data should be transformed (i.e., using arcsin or ln transformation) for use with parametric statistics [64].

Although the protocols that provide data suitable for discrimination ratio calculations do provide an indication of preference, they do not account for individual differences in the total time that subjects spend investigating the objects. For example, one mouse may spend only 20 s investigating objects during a five-minute training period, whereas another may spend 120 s. A subject that spends 120 s exploring the objects is likely to form a more lasting memory of the objects than a subject that spends only 20 s exploring the objects. Therefore, it can be difficult to estimate the extent to which exploration time during training affects exploration time during testing. To eliminate this confound, some investigators require a set amount of time spent investigating the objects during training only [21] or during both training and testing [140]. Using this method, time spent with the objects is compared to chance performance [10,12,34,79]. For example, our laboratory requires that subjects explore the two objects for a total of 30 s during both training and testing, and gives subjects up to 20 min to reach this criterion. We then use a one-sample t-test to compare exploration time to the chance value of 15 s, which reflects an identical amount of time spent with both objects. We use this protocol because controlling for exploration time during training is important in our experimental designs. However, trial time is often fixed in studies using pre-training treatments to ensure that the time from treatment to testing and amount of drug in circulation during training and testing is the same for all subjects. Ultimately, whether interpreting the results of an experiment or designing an experiment of one's own, it is important to consider the way in which the experiment was designed in order to understand how hormones, or any other experimental manipulation, affect memory measured by OR and OP.

5. Performance of gonadally intact female rodents in object memory tasks

5.1. The estrous cycle

Studying the influence of endogenous E_2 and P_4 levels on hippocampal memory in gonadally intact females is inherently challenging in light of the naturally fluctuating hormones levels across the 4–5 day estrous cycle and the multi-day protocols typically used to test learning and memory. As such, very few studies have examined the effects of E_2 and P_4 on hippocampal memory in gonadally intact females. However, some investigators have capitalized on the one-trial nature of OR and OP to test the effects of cyclic hormone fluctuations on hippocampal memory (Table 1). In these protocols, training and testing occurred on the same day to ensure that both phases were conducted within the same estrous phase. When tested 1 h after training, female rats in any phase of the cycle displayed intact OR memory, whereas only those in estrus (low E_2 and P_4 levels) exhibited intact OP memory [141]. Other investigators report greater differences among cycle phases when OR and OP testing were conducted 4 h after training. In these studies, rats or mice in proestrus (elevated E_2 and P_4 levels) displayed enhanced OR memory relative to their counterparts in estrus or diestrus (reduced E_2 and P_4 levels) [129,142,143]. Similarly, rats in proestrus exhibited better spatial memory in OP than rats in

diestrus [143,144]; however, rats in estrus did as well [144]. This curious finding, combined with the OP data from Sutcliffe et al. [141], suggests that perhaps the P_4 generated by the corpus luteum during estrus is more beneficial for spatial memory than for object recognition. Based on the data from these few studies, it is tempting to speculate that memory in OR and OP is facilitated during the estrous cycle when E_2 and P_4 are elevated, but definitive conclusions about cyclic fluctuations in object memory will require further study.

5.2. Pregnancy

E_2 and P_4 are also naturally elevated during pregnancy, which influences hippocampal morphology and memory [93,145]. For example, CA1 dendritic spine density is significantly higher in pregnant and lactating female rats than in virgin females at any stage of the estrous cycle [146]. Furthermore, reproductively experienced middle-aged female rats exhibit more cell proliferation in the dentate gyrus in response to exogenous E_2 than virgin females of the same age, suggesting that reproductive experience may potentiate the hippocampal response to E_2 later in life [147]. Behaviorally, pregnant females with high endogenous E_2 and P_4 levels exhibited enhanced memory in the OR and OP tasks relative to non-pregnant females [143] (Table 1), although other studies find that memory in different hippocampal-dependent tasks is impaired during pregnancy [93]. Interestingly, number of pregnancies also plays a role in object memory, as multiparous rats (females with $\geq$2 pregnancies) demonstrate enhanced OP memory relative to primiparous (first-time pregnancy) rats [144]. Moreover, OP was enhanced in post-partum and lactating rats relative to rats in their first trimester [144], suggesting that the hormonal milieu in late pregnancy and the early post-partum period may facilitate spatial memory. Although these data are consistent with findings for other hippocampal-dependent spatial tasks such as the radial arm maze [148], other studies contradict these findings [93,145].

5.3. Caveats

Inconsistencies among studies examining gonadally intact female rodents may be due to numerous factors, including the fact that so few labs are engaged in this research. With such a small literature, differences in methods, species, and strains are likely to be magnified in importance. However, these discrepancies also likely reflect the inherent difficulty of trying to examine the behavioral effects of hormones in subjects whose hormone state is in nearly constant flux across a pregnancy or a natural estrous cycle. For this reason, most investigators opt to eliminate natural hormonal variability by ovariectomizing their female subjects, thereby allowing investigators to focus their attention on the effects of exogenous hormone treatment in the absence of hormone fluctuations. As such, the literature on the effects of E_2 and P_4 on hippocampal memory in ovariectomized females is considerably more extensive than that on gonadally intact females. Although ovariectomy is easier than managing the natural cycle and allows for more control of hormone levels, it is unclear if these two models are truly comparable. For example, it is unknown if an exogenous E_2 injection would have a similar effect on object memory in an ovariectomized female and a gonadally intact female in estrus. Serum E_2 levels would be low in both females prior to injection, but one has ovarian tissue that can be stimulated by the exogenous injection and the other does not. It is unknown whether the presence of functioning ovaries makes a difference in the mnemonic responsiveness to exogenous hormones, but this is a key question because most women who take hormones possess an intact reproductive system. Unfortunately, this issue has not been addressed for object memory or any other type memory. Pharmacological depletion of ovarian follicles by 4-vinylcyclohexene-diepoxide (VCD) results in a gradual loss of ovarian function, so this treatment could be a useful alternative to traditional ovariectomy surgery. In middle-aged rats, VCD-induced follicular depletion was less detrimental for spatial working memory in a water-based radial arm maze task than ovariectomy surgery [99]. However, middle-aged VCD-treated rats given conjugated equine estrogens had significantly worse spatial working memory in the water radial arm maze than middle-aged ovariectomized rats [100], suggesting that VCD-treatment and ovariectomy have fundamentally different effects on the response to exogenous E_2 in aging females. Yet very few studies have used VCD, so it is premature to make any conclusions about the effects of this treatment on memory function. Nevertheless, it is important to note that this potential alternative to ovariectomy could help in understanding how ovarian function and ovarian loss may influence the mnemonic response to exogenous hormone treatment.

The majority of ovariectomy studies have examined effects of ovarian hormones on spatial tasks, such as the Morris water maze, radial arm maze, and T-maze. However, a substantial number of studies from the past decade have examined effects of E_2 and P_4 on OR and OP memory in adult female rats and mice of various ages. The remaining sections of this review will discuss these findings in detail.

6. Hormone replacement in young ovariectomized females

6.1. Effects of ovariectomy on OR and OP

Given the effects of circulating ovarian hormones on OR and OP in gonadally intact rodents, one might ask whether ovariectomy itself has detrimental effects on memory in these tasks. Few studies have addressed this issue directly, but the data indicate that ovariectomy impairs memory in both tasks. One study of ovariectomized rats and gonadally intact sham-operated rats tested memory in the OR and OP tasks weekly for seven weeks after surgery, which was conducted at approximately 2.5 months of age [149]. For both tasks, ovariectomy produced a significant and persistent deficit; for OR, the deficit became evident two weeks after surgery, and for OP, the deficit became evident four weeks after surgery [149]. For both tasks, the deficit persisted throughout the seven weeks of testing [149]. These deficits were associated with a reduction in pyramidal neuron dendritic spine density in hippocampal CA1 and the medial prefrontal cortex [149], suggesting a role for morphological alterations in the observed memory deficits. These findings are supported by other recent studies demonstrating that ovariectomy for extended periods impairs memory and reduces the response to exogenous E_2 [180]. In one study, two month-old female mice ovariectomized one week prior to OR training outperformed mice that had been ovariectomized without E_2 or P_4 replacement for six or 12 weeks [150]. This impairment was reversed by five weeks of chronic systemic E_2 treatment, suggesting that the young female mouse brain remains responsive to E_2 for at least three months after ovariectomy. However, longer periods of ovarian hormone deprivation diminish responsiveness to E_2, as illustrated by data from rats ovariectomized at two months of age for a duration of 9, 15, or 19 months prior to E_2 treatment. Acute pre-training injections of E_2 enhanced OR memory in rats ovariectomized for 9 or 15 months [16], which is consistent with other studies by these investigators demonstrating that E_2 treatment 9 or 15 months after ovariectomy also increased LTP, CA1 dendritic spine density, GluN2B-mediated neurotransmission, and NMDA/AMPA ratio [16,151–153]. In contrast, E_2 did not enhance memory or increase hippocampal function in rats ovariectomized for 19 months prior to E_2 treatment [151–153]. One potential explanation of this finding is that the rats were too old to respond to E_2, as

the rats were about 21 months old at the time of testing. However, E_2 could enhance memory in 21 month-old rats ovariectomized only one month prior to treatment [16], suggesting a greater role of length of hormone deprivation than age on the response to E_2 delivered prior to training. Overall, these studies demonstrate a detrimental effect of ovariectomy on memory in the OR and OP tasks, with greater impairments observed after longer lengths of ovarian hormone deprivation.

6.2. Effects of E_2 on OR and OP in young ovariectomized females

The aforementioned detrimental effects of ovarian hormone deprivation are reversible with systemic or intracranial administration of exogenous E_2 (Table 2). Systemic injections of E_2 in young ovariectomized rats and mice in the range of 15 μg/kg to 0.2 mg/kg dose-dependently enhance OR [62,69,150,154–157], and OP [62,69,155] when given prior to training. These enhancements were observed after chronic or acute E_2 treatments. However, such pre-training treatments can affect non-mnemonic aspects of task performance (e.g., motivation, anxiety, motor behavior) that can confound interpretation of behavioral outcomes and should be accounted for when interpreting results. Further, pre-training treatments do not permit a distinction between memory acquisition and consolidation [158]. Therefore, several laboratories, including our own, have administered E_2 immediately post-training, which allows effects on memory consolidation to be isolated in the absence of non-mnemonic performance confounds. In these studies, systemic E_2 (15 μg/kg to 0.2 mg/kg) administered immediately after training enhanced both OR [15,80,133,155,159–164] and OP [155,163,164], indicating that E_2 specifically enhances object recognition and spatial memory consolidation. Interestingly, immediate post-training systemic injections of other estrogens, including 17α-estradiol and the synthetic diethylstilbestrol, also enhanced OR and OP memory [155,164], suggesting that multiple forms of estrogens can facilitate object recognition and spatial memory. Moreover, E_2's ability to facilitate memory consolidation is restricted to an approximate 1 h window after training, as rats and mice treated with E_2 1–3 h post-training do not remember the familiar or unmoved objects during OR or OP testing [10,129,144]. These data are significant, as they demonstrate that E_2 can enhance OR and OP within the brief time window during which memory consolidation occurs in these tasks.

It is important to note that systemic treatments have the primary disadvantage of affecting tissues throughout the body, so the role of the hippocampus in these memory enhancements is unclear. Therefore, our laboratory has conducted a series of studies in which we bilaterally infused 5 μg E_2 directly into the dorsal hippocampus to pinpoint the role of this structure in hormonal regulation of OR and OP memory consolidation. We have found that bilateral dorsal hippocampal infusion of E_2 immediately post-training enhances both OR and OP memory consolidation in young ovariectomized mice [10,12,34,35,79], thereby demonstrating that the dorsal hippocampus plays a major role in mediating E_2's effects on object recognition and spatial memory consolidation. A study from another laboratory recently confirmed this finding in two different strains of mice [15], including the C57BL/6 strain used for our studies.

Collectively, the literature on E_2 and object memory in rodents shows that systemic or intrahippocampal administration of E_2 consistently enhances memory in the OR and OP tasks when given prior to or after training. These effects generalize across various OR and OP protocols conducted in different labs in different rodent species (rats and mice). Importantly, E_2 must be administered during acquisition or within a one-hour window immediately after training to enhance memory consolidation. Finally, E_2 infusion restricted to the dorsal hippocampus enhances OR and OP memory consolidation, indicating a crucial role of this structure in the hormonal modulation of object memory in females.

6.3. Effects of P_4 on OR and OP in young ovariectomized females

Although the majority of studies have focused on E_2 replacement, some investigators have also examined the effects of P_4, alone or in combination with E_2, on OR and OP (Table 3). As mentioned above, P_4 administered systemically prior to training impairs or has no effect on various forms of hippocampal memory in tasks such as the radial arm maze, footshock avoidance, and Morris water maze [121,122,126,128]. These effects typically depend on dose and method of administration (e.g., cyclic or continuous). However, P_4 administered systemically (4–20 mg/kg) immediately after training dose-dependently enhances OR in young ovariectomized female rodents [127,129,144,165–167]. These effects are supported by other work from our laboratory in which 0.01, 0.1, or 1 μg P_4 infused directly into the dorsal hippocampus enhanced OR in a manner dependent on rapid hippocampal cell signaling [87,168].

In contrast, fewer studies have examined the effects of P_4 on spatial memory tested in OP, and these data are conflicting. For example, in one study, 4 mg/kg P_4 given immediately post-training enhanced OP in young ovariectomized mice [165], however, another post-training study found that 10 mg/kg did not enhance OP in young ovariectomized rats [167]. These differences could be due to numerous factors, including dose of P_4 and/or species. However, the fact that ovariectomized female rats treated with the P_4 metabolite 3α,5α-THP immediately after training also exhibited enhanced OR and OP memory relative to vehicle-treated rats [129,144], may suggest a dose-dependent effect of P_4 on OP. Clearly, more research is needed on this subject. Finally, P_4 must be given within 2 h after object training in order to facilitate object memory consolidation [129,144,168], supporting the role of P_4 in mediating memory formation during the memory consolidation window.

Several studies have co-administered E_2 and P_4 to mimic peak hormone levels observed during the proestrus phase of the estrous cycle. Ovariectomized rats treated with systemic E_2 (0.9 mg/kg) and P_4 (4 mg/kg) immediately after object training exhibited enhanced OR and OP memory relative to vehicle-treated rats [129,144]. In ovariectomized mice, we found that systemic E_2 (0.2 mg/kg) and P_4 (10 or 20 mg/kg) given immediately after training enhanced OR memory consolidation [133]. However, a 5 mg/kg dose of P_4 blocked the memory-enhancing effects of E_2 in this study, highlighting the dose-dependency of P_4's effects on memory observed in our previous work [127], even when paired with E_2. In general, these data suggest that high levels of $E_2 + P_4$ are beneficial for object memory consolidation in young female rodents, but more work is needed to elucidate optimal dose ranges and timing of injection, as well as the specificity of these effects to the hippocampus.

7. Molecular mechanisms in the dorsal hippocampus underlying the beneficial effects of E_2 and P_4 on object memory

Numerous molecular mechanisms within the hippocampus are likely involved in the hormonal regulation of object memories. As discussed in Section 3 above, E_2 and P_4 may act via classical or non-classical mechanisms to alter hippocampal spinogenesis, neurogenesis, excitability, synaptic plasticity, cell signaling, epigenetic processes, and gene expression. Many of the rapid effects of these hormones on object memory have recently been attributed to non-classical actions of E_2 and P_4 (see below). However, some effects may also involve classical actions of these hormones, which could

Table 2
Effects of exogenous estradiol on object memory in young adult female rodents.

Species	Type of hormone	ROA	Timing of administration[a]	Task(s)	Effect on OR and/or OP	Ref. no.	Reference
Rat	17α-E_2, E_2, DES	Systemic	Pre-training	OR, OP	Injection of 17α-E_2, E_2, or DES (15 μg/kg) 30 min before training enhanced OR and OP	[155]	Luine et al. (2003)
Rat	EB	Systemic	Pre-training	OR, OP	Two injections of EB (50 μg/kg) two days before training enhanced OR and OP	[154]	Jacome et al. (2010)
Rat	E_2	Systemic	Pre-training	OR	Two injections of 10 μg E_2 24 or 48 h before training enhanced OR	[156]	Vedder et al. (2013)
Mouse	E_2	Systemic	Pre-training	OR, OP	Injection of E_2 (1.5–3 μg/kg) 15 min before training enhanced OR and OP	[62]	Phan et al. (2012)
Mouse	E_2	Systemic	Pre-training	OR, OP	Six or 10 weeks of E_2 silastic (50 μg/25 μl) enhanced OR and OP	[157]	Ismail and Blaustein (2013)
Mouse	E_2	Systemic	Pre-training	OR	Five weeks of E_2 silastic (0.18 mg/4 μl) enhanced OR	[150]	Fonseca et al. (2013)
Mouse	EB	Systemic	Pre-training	OP	EB (1 μg/day) for 5 days before training enhanced OP	[69]	Li et al. (2004)
Rat	E_2, DES	Systemic	Post-training	OR, OP	E_2 (30 μg/kg) enhanced OR and OP; DES (15 μg/kg) enhanced OR, but not OP	[155]	Luine et al. (2003)
Rat	17α-E_2, E_2	Systemic	Post-training	OR, OP	Doses of 5–20 μg/kg E_2 enhanced OR or OP; doses of 1–5 μg/kg 17α-E_2 enhanced OR or OP	[164]	Inagaki et al. (2010)
Rat	E_2	Systemic	Post-training	OR	E_2 (0.9 mg/kg) enhanced OR, but not if delayed 1 h after training	[129]	Walf et al. (2006)
Rat	E_2	Systemic	Post-training	OP	E_2 (0.9 mg/kg) enhanced OP, but not if delayed 1.5 h after training	[144]	Frye et al. (2007)
Mouse	Water-soluble E_2	Systemic	Post-training	OR	E_2 (0.2 mg/kg) enhanced OR	[159]	Gresack and Frick (2004)
Mouse	Water-soluble E_2	Systemic	Post-training	OR	E_2 (0.2 and 0.4 mg/kg) enhanced OR	[160]	Gresack and Frick (2006)
Mouse	Water-soluble E_2	Systemic	Post-training	OR	E_2 (0.2 mg/kg) enhanced OR	[161]	Gresack et al. (2007)
Mouse	Water-soluble E_2	Systemic	Post-training	OR	E_2 (0.2 mg/kg) enhanced OR	[162]	Gresack et al. (2007)
Mouse	Water-soluble E_2	Systemic	Post-training	OR	E_2 (0.2 mg/kg) enhanced OR	[80]	Lewis et al. (2008)
Mouse	E_2	Systemic	Post-training	OR, OP	E_2 (0.1 mg/kg) enhanced OR, OP in wild type mice, but not ERβ knockouts	[163]	Walf et al. (2008)
Mouse	Water-soluble E_2	Systemic	Post-training	OR	E_2 (0.2 mg/kg) enhanced OR	[133]	Harburger et al. (2009)
Mouse	Water-soluble E_2	Systemic	Post-training	OR	E_2 (0.2 mg/kg) enhanced OR in wild type and ERα knockout mice, but not in ERβ knockouts	[178]	Frick et al. (2010)
Mouse	Water-soluble E_2	Systemic, Intra-hippocampal	Post-training	OR	E_2 (0.2 mg/kg or 5 μg infused bilaterally into the dorsal hippocampus) enhanced OR	[15]	Pereira et al. (2014)
Mouse	Water-soluble E_2	Intra-hippocampal	Post-training	OR	5 μg E_2 infused bilaterally into the dorsal hippocampus enhanced OR, but not if delayed 3 h after training	[10]	Fernandez et al. (2008)
Mouse	Water-soluble E_2	Intra-hippocampal	Post-training	OR	5 μg E_2 infused bilaterally into the dorsal hippocampus enhanced OR	[79]	Zhao et al. (2010)
Mouse	Water-soluble E_2	Intra-hippocampal	Post-training	OR	5 μg E_2 infused bilaterally into the dorsal hippocampus enhanced OR	[35]	Zhao et al. (2012)
Mouse	Water-soluble E_2	Intra-hippocampal	Post-training	OR	5 μg E_2 infused bilaterally into the dorsal hippocampus enhanced OR	[34]	Fortress et al. (2013)
Mouse	Water-soluble E_2	Intra-hippocampal	Post-training	OR, OP	5 μg E_2 infused bilaterally into the dorsal hippocampus enhanced OR and OP	[12]	Boulware et al. (2013)

Note: ROA = route of administration; OR = object recognition; OP = object placement; DES = diethylstilbestrol; EB = estradiol benzoate.
[a] Post-training treatments were given immediately after training unless indicated otherwise in the "Effect on OR and/or OP" column.

Table 3
Effects of exogenous progestins on object memory in young adult female rodents.

Species	Type of hormone	ROA	Timing of administration[a]	Task(s)	Effect on OR and/or OP	Ref. no.	Reference
Progesterone							
Rat	P_4, 3α,5α-THP	Systemic	Post-training	OR	P_4 (4 mg/kg) enhanced OR, but not if delayed 1 h after training; 3α,5α-DHT (4 mg/kg) enhanced OR	[129]	Walf et al. (2006)
Rat	P_4, 3α,5α-THP	Systemic	Post-training	OP	P_4 (4 mg/kg) enhanced OP, but not if delayed 1.5 h after training; 3α,5α-DHT (4 mg/kg) enhanced OP	[144]	Frye et al. (2007)
Rat	P_4	Systemic	Post-training	OR	P_4 (4 mg/kg) enhanced OR	[166]	Frye et al. (2009)
Mouse	P_4	Systemic	Post-training	OR, OP	P_4 (10 mg/kg) enhanced OR, but not if delayed 1.5 h after training; no effect on OP	[167]	Frye and Walf (2008)
Mouse	P_4, 3α,5α-THP, MPA	Systemic	Post-training	OR, OP	P_4 and 3α,5α-DHT (4 mg/kg) post-training enhanced OR and OP, but MPA (10 mg/kg) did not	[165]	Frye et al. (2013)
Mouse	Water-soluble P_4	Systemic	Post-training	OR	P_4 (10 or 20 mg/kg) enhanced OR	[127]	Harburger et al. (2008)
Mouse	Water-soluble P_4	Intra-hippocampal	Post-training	OR	P_4 (0.01–1 μg) enhanced OR, but not if delayed 2 h after training	[168]	Orr et al. (2009)
Mouse	Water-soluble P_4	Intra-hippocampal	Post-training	OR	P_4 (0.1 μg) enhanced OR	[87]	Orr et al. (2012)
Estradiol plus progesterone							
Rat	E_2, P_4	Systemic	Post-training	OR	E_2 (0.9 mg/kg) + P_4 (4 mg/kg) enhanced OR, but not if delayed 1 h after training	[129]	Walf et al. (2006)
Rat	E_2, P_4	Systemic	Post-training	OP	E_2 (0.9 mg/kg) + P_4 (4 mg/kg) enhanced OP, but not if delayed 1.5 h after training	[144]	Frye et al. (2007)
Mouse	Water-soluble E_2, P_4	Systemic	Post-training	OR	E_2 (0.2 mg/kg) + P_4 (10 or 20 mg/kg) enhanced OR; E_2 (0.2 mg/kg) + P_4 (5 mg/kg) did not enhance OR	[133]	Harburger et al. (2009)

Note: ROA = route of administration; OR = object recognition; OP = object placement; 3α,5α-THP = 3α,5α-tetrahydroprogesterone; MPA = medroxyprogesterone acetate.
[a] Post-training treatments were given immediately after training unless indicated otherwise in the "Effect on OR and/or OP" column.

lead to changes in hippocampal function that have been observed to last for months [115]. Effects of E_2 and P_4 outside of the hippocampus must be also considered. Abundant evidence suggests that E_2 enhances cholinergic function in basal forebrain neurons that project to the hippocampus [97]. Basal forebrain cholinergic changes in response to E_2 can occur within minutes of application (e.g., potassium-evoked acetylcholine release) or after many days or weeks of treatment (e.g., choline acetyltransferase mRNA or activity, high affinity choline uptake, cholinergic neuron number, muscarinic receptor binding) [169–173], so both classical and non-classical mechanisms could mediate these effects. Although the importance of these basal forebrain cholinergic neurons to hippocampal memory has been subject to debate [174], potentiation of basal forebrain cholinergic function seems to play a role in the beneficial effects of E_2 on hippocampal spatial memory in the radial arm and Morris water mazes [102,106,107,175]. However, the role of basal forebrain cholinergic neurons to OR and OP memory is unclear, as the only study to examine this subject found that the effects of E_2 on OR in mice were not related to changes in basal forebrain muscarinic receptors [176].

At present, it is unclear how much classical ER or PR mechanisms contribute to the effects of E_2 and P_4 on object memory because these mechanisms have not been specifically blocked in memory studies to date; receptor knockouts or antagonists also block non-classical effects of ERs and PRs. However, non-classical effects of E_2 and P_4 on cell-signaling pathways or epigenetic processes can be pinpointed using inhibitors of specific rapid processes such as enzyme phosphorylation or histone acetylation (it is important to note that doses used in these inhibitor experiments do not affect memory on their own so that interactions between hormone and inhibitor can be observed). As such, there is a much better understanding of the non-classical mechanisms underlying rapid consolidation of OR and OP memories. These data will be the focus of the discussion below.

7.1. Estrogen receptors

The beneficial effects of estrogens on hippocampal memory are likely mediated through classical ERs (ERα and ERβ), as well as non-classical membrane receptors (e.g., GPER, ER-X, Gq-mER) [41,82,177]. Although some evidence does implicate non-classical ERs in mediating OR and OP memory [178,179], the involvement of specific non-classical ERs remains unclear. Much more is known about the roles of classical ERs in object memory, which have been tested in young ovariectomized rodents using specific ER agonists and ER knockouts. The majority of behavioral studies using ER agonists implicate ERβ in mediating the memory-enhancing effects of E_2 on OR and/or OP [12,15,64,129,154,163,178], although no effect of the ERβ agonist diarylpropionitrile (DPN) has been reported for OP in rats [144], or for OR and OP in Swiss mice [15] (Table 4). Interestingly, several studies found beneficial effects of ERβ agonists, but not ERα agonists, on OR and/or OP. For example, one report found that systemic pre-training delivery of the ERβ agonists Compound 19 (C19) or DPN enhanced both OR and OP, whereas the ERα agonist propyl pyrazole triol (PPT) did not [154,178]. Moreover, unlike female wild type or ERα knockout mice, ERβ knockout mice do not exhibit enhanced OR or OP memory following systemic post-training treatment with E_2 [163,178], further supporting a role for ERβ, rather than ERα, in mediating object recognition and spatial memories. Consistent with this notion, E_2-treated ERβ knockout mice are impaired in other hippocampal-dependent tasks, including the Morris water maze [181] and Y-maze [182]. However, other data suggest a possible role for ERα, particularly in the dorsal hippocampus [12,15,64,144]. For example, systemic PPT and DPN dose-dependently enhanced OR and OP when given pre-training [64] or post-training [129]. Recently, low does of PPT and DPN infused into the dorsal hippocampus immediately post-training were shown to enhance OR and OP in C57BL/6 mice [12,15]. These behavioral effects are supported at the cellular level by studies

Table 4
Effects of exogenous estrogen receptor agonists on object memory in young adult female rodents.

Species	Type of hormone	ROA	Timing of administration[a]	Task(s)	Effect on OR and/or OP	Ref. no.	Reference
Rat	PPT, DPN, C-19	Systemic	Pre-training	OR, OP	Two injections of DPN (3 mg/kg) or C-19 (5 mg/kg), but not PPT (3 or 5 mg/kg), two days before training enhanced OR and OP	[154]	Jacome et al. (2010)
Mouse	PPT, DPN	Systemic	Pre-training	OR, OP	PPT (75 μg) 15 min before training enhanced OR and OP, effects of DPN depended on dose and task difficulty	[64]	Phan et al. (2011)
Rat	PPT, DPN	Systemic	Post-training	OR	PPT and DPN (0.9 mg/kg) enhanced OR	[129]	Walf et al. (2006)
Rat	PPT, DPN	Systemic	Post-training	OP	PPT (0.9 mg/kg), but not DPN (0.9 mg/kg), enhanced OP	[144]	Frye et al. (2007)
Mouse	DPN	Systemic	Post-training	OR, OP	DPN (0.1 mg/kg) enhanced OR and OP in wild type mice, but not ERβ knockouts	[163]	Walf et al. (2008)
Mouse	PPT, DPN	Systemic	Post-training	OR	DPN (0.5 mg/kg), but not PPT (0.5 mg/kg), enhanced OR	[178]	Frick et al. (2010)
Mouse	PPT, DPN	Intra-hippocampal	Post-training	OR, OP	PPT (0.1 pg) and DPN (10 pg) enhanced OR and OP	[12]	Boulware et al. (2013)
Mouse	PPT, DPN	Intra-hippocampal	Post-training	OR	PPT (0.1 pg) and DPN (10 pg) enhanced OR in C57BL/6 mice; PPT, but not DPN, enhanced OR in Swiss mice	[15]	Pereira et al. (2014)

Note: ROA = route of administration; OR = object recognition; OP = object placement; PPT = propyl pyrazole triol; DPN = diarylpropionitrile. C-19 = compound 19.
[a] Post-training treatments were given immediately after training unless indicated otherwise in the "Effect on OR and/or OP" column.

demonstrating that systemic administration of estradiol benzoate, PPT, or DPN can upregulate hippocampal expression of synaptophysin and spinophilin [183], synaptic proteins that help support and maintain synaptic connections important for memory formation and storage. Collectively, this work suggests that either ERα or ERβ may mediate the effects of E_2 on object memory, although the contradictory evidence for ERα necessitates more research to better pinpoint the involvement of ERα in object memory consolidation.

7.2. Cell-signaling pathways

As discussed above, many effects of sex steroid hormones are thought to occur via rapid non-classical mechanisms that activate cell signaling in the brain. These data have been reviewed in detail elsewhere [39,95,177,184] and, therefore, will be only briefly summarized here (see Fig. 2 for a schematic illustration). One way in which ERα and ERβ can initiate rapid cell signaling is by interacting with non-steroidal membrane receptors like neurotransmitter receptors. Our laboratory recently used bilateral dorsal hippocampal infusions of PPT and DPN given immediately post-training to demonstrate that ERα and ERβ enhance OR and OP in female mice in a manner dependent on activation of metabotropic glutamate receptor 1a (mGluR1a) [12]. We had previously shown that rapid activation of the ERK cell-signaling pathway in the dorsal hippocampus is necessary for E_2 to enhance OR in young ovariectomized mice [10]. The importance of ERK phosphorylation in the effects of E_2 on OR are underscored by other findings from our laboratory showing that dorsal hippocampal activation of PI3K/Akt signaling upstream from ERK and mammalian target of rapamycin (mTOR) signaling downstream from ERK are also necessary for E_2 to enhance OR in young ovariectomized mice [34,80]. The E_2-induced activation of mTOR by ERK is notable given mTOR's important role in initiating local protein synthesis in hippocampal dendrites [185]. Our recent work extended these findings to show that inhibition of mGluR1a activation prevented E_2, PPT, and DPN from activating dorsal hippocampal ERK signaling and from enhancing OR and OP memory consolidation [12]. These data suggest that E_2 activates cell-signaling cascades by binding to ERα or ERβ, which then interact with mGluR1a to initiate cell signaling. ERs may interact

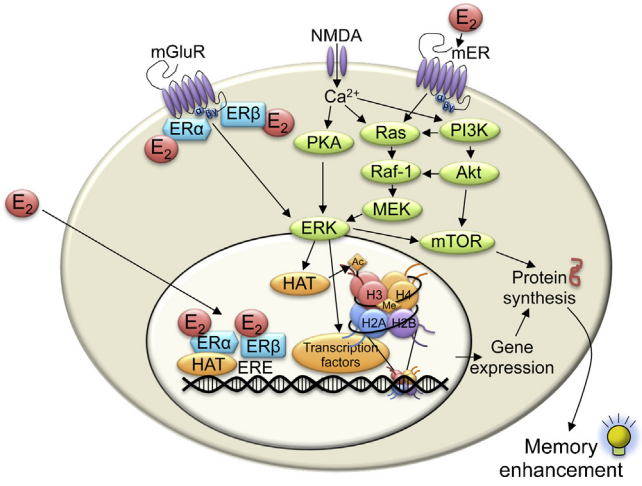

Fig. 2. Schematic illustration of the molecular mechanisms in the hippocampus thus far identified to be required for E_2 to enhance object memory consolidation. In the classical response, E_2 binds ERα and ERβ, which then translocate into the nucleus, bind to the estrogen response element (ERE) on DNA, and interact with co-regulatory proteins (including histone acetyltransferases, HAT) to influence transcription. E_2 also affects cell signaling in several non-classical ways. It can bind to ERs that interact with metabotropic glutamate receptors (mGluRs) at the membrane and activate extracellular regulated kinase (ERK) signaling. It can also interact with NMDA receptors and membrane-bound ERs (mER) to activate the protein kinase A (PKA), phosphoinositol-3-kinase (PI3K), and mammalian target of rapamycin (mTOR) signaling pathways. mTOR signaling regulates the protein synthesis necessary for memory formation. Activation of ERK increases H3 acetylation. Both H3 acetylation and DNA methylation are necessary for E_2 to enhance memory consolidation. Adapted with permission from Frick [184] and Fortress and Frick [177].

with additional glutamate receptors, such as NMDA receptors, as suggested by other data from our laboratory showing that post-training dorsal hippocampal administration of the NMDA receptor antagonist APV prevents systemic E_2 (0.2 mg/kg) from enhancing OR memory in young ovariectomized mice [80]. Moreover, inhibiting cell signaling downstream from NMDA receptors with the cAMP inhibitor Rp-cAMPs also prevented systemic E_2 from

enhancing OR, suggesting that ERα or ERβ may also interact with NMDA receptors to the initiate rapid cell signaling necessary for hippocampal object memory consolidation.

7.3. Epigenetics

ERK activation can regulate cellular processes in numerous ways. As mentioned above, ERK activates mTOR, which phosphorylates core components of the protein synthesis machinery to initiate protein translation [186]. Perhaps better known is the ability of ERK to regulate gene transcription by phosphorylating the transcription factor cAMP response-element binding protein (CREB; [187]), which interacts with histone acetyltransferase enzymes to promote transcription [188]. Indeed, ERK-dependent regulation of epigenetic processes such as histone acetylation is essential for long-term hippocampal memory formation [35,189]. DNA is tightly coiled around 4 core histone proteins (H2A, H2B, H3, H4), each of which has a tail that can be post-translationally modified to produce transcriptionally permissive or repressive states [190]. Histone acetyltransferases (HATs) add acetyl groups to histone tails, whereas histone deacetylases (HDACs) remove them [191]. OR memory consolidation is enhanced by HDAC inhibitors [79,192] and impaired by HAT inhibitors [35]. Contextual fear conditioning or ERK activation increases acetylation of H3 in the hippocampus, and inhibiting ERK activation in the dorsal hippocampus blocks H3 acetylation [189]. Our laboratory recently demonstrated that E_2 increases H3 acetylation in an ERK-dependent manner, and that the ability of post-training dorsal hippocampal infusion of E_2 to enhance OR memory consolidation is dependent on histone acetylation [35,79]. E_2 also influences OR memory by suppressing negative regulators of memory, such as HDAC2 and HDAC3. These HDACs exert detrimental effects on hippocampal memory by removing acetyl groups from histone tails, thereby preventing the relaxed chromatin state that is essential for gene transcription [193–195]. HDAC2 levels are significantly reduced in the dorsal hippocampus after E_2 treatment in young ovariectomized mice [35,79], and both HDAC2 and HDAC3 levels are reduced after E_2 treatment in middle-aged females [196]. As such, E_2 promotes a suite of histone alterations that facilitate acetylation and the transcriptionally permissive state that allows for gene transcription and object memory enhancement.

E_2's effects on OR memory consolidation are also regulated, in part, by DNA methylation, an epigenetic process that generally silences gene transcription by adding methyl groups to certain cytosine residues on the DNA. Three DNA methyltransferases (DNMTs) catalyze the methylation reaction: DNMT1 is a maintenance enzyme that moves existing methyl groups during replication, whereas DNMT3A and DNMT3B are de novo methyltransferases that add new methyl marks to the DNA [197]. Interestingly, blocking hippocampal DNMT activation with the DNMT inhibitor 5-AZA immediately, but not 3 h, after training enhances OR memory consolidation in young ovariectomized mice [79]. These data suggest that preventing the methylation of genes necessary for memory formation (e.g., *reelin*) is instrumental for OR memory. With respect to E_2, we found that dorsal hippocampal infusion of E_2 increases DNMT3B mRNA and protein in the dorsal hippocampus, and the ability of post-training dorsal hippocampal infusion of E_2 to enhance OR memory consolidation is blocked by 5-AZA [79]. These data suggest that E_2 may enhance OR memory by methylating memory suppressor genes like those for *Hdac2* or *Hdac3*. Collectively, these data suggest that E_2 may mediate its beneficial effects on memory by increasing acetylation of memory supporting genes and increasing methylation of memory suppressing genes, processes that may ultimately act in concert to facilitate the transcription and translation of genes important for neural plasticity and the consolidation of object memories.

7.4. Progesterone

The molecular mechanisms through which P_4 affects hippocampal memory consolidation are not nearly as well characterized as those of E_2. However, some data suggest that P_4 regulates OR memory via similar cell signaling mechanisms as E_2. For example, P_4 promotes rapid activation of the ERK [87,198], PI3K [198], and PKA [199] cell-signaling pathways. Our laboratory has shown that the ability of a post-training dorsal hippocampal infusion of P_4 to enhance OR memory consolidation in young ovariectomized mice is dependent on rapid dorsal hippocampal activation of ERK and mTOR [87]. These findings suggest that P_4 may regulate memory via similar cell-signaling mechanisms as E_2. However, potential progesterone receptor mechanisms mediating these effects are unclear. Our unpublished work suggests that dorsal hippocampal activation of either classical PRs or mPRs enhances OR memory consolidation in young ovariectomized mice [200], although possibly through different cell-signaling mechanisms. That is, mPRs appear to activate ERK/mTOR signaling, whereas classical PRs appear to activate canonical Wnt signaling [200]. Finally, it is possible that P_4's effects on memory and cell signaling are entirely independent of PRs, and rather stem from the actions of P_4 metabolites such as allopregnanolone, androgens, and estrogens on $GABA_A$, androgen, and estrogen receptors, respectively. As such, much more work must be conducted to gain a better understanding of the molecular mechanisms underlying P_4's effects on object memory consolidation.

8. Regulation of object memory in aging females

In women, menopause occurs in the early 50s and is characterized by the cessation of reproductive function due to a sharp decline in circulating estrogens and progestins. In rodents, regular estrous cycling also declines in middle age due to age-related reductions in E_2 and P_4 levels, and the transition from normal to abnormal cycling has been associated with the onset of hippocampal memory decline [201,202]. Ovarian hormones play a significant role in hippocampal neuroprotection [203–206], so the loss of these hormones during aging renders the hippocampus particularly susceptible to neurodegeneration and dysfunction [207–209]. Therefore, it should come as no surprise that memory in hippocampal tasks suffers in females as a consequence of aging. Most relevant to this discussion, one recent study capitalized on variability in the timing of reproductive senescence in rats to examine the relationship between reproductive cycling and OR memory. This study found that rats in early middle-age (12 months old) with compromised reproductive status (declining fertility, fecundity, and cycle regularity) and lower circulating levels of ovarian hormones, exhibited worse memory in the OR task than age-matched female rats with maintained reproductive status [210]. Furthermore, as will be discussed below, the responsiveness of the brain to ovarian hormone administration appears to diminish with advanced age.

Ovariectomized rodents in middle age (approximately 14–19 months of age) appear to be as responsive to exogenous E_2 as young females (Table 5). For example, systemic E_2 or conjugated equine estrogens given pre- or post-training generally enhance OR and OP in middle-aged rats and mice [16,161,211,213] [but see [146]]. Furthermore, dorsal hippocampal infusion of E_2 given immediately post-training enhances OR memory in a manner dependent on ERK and PI3K activation [81], as in young females [34]. Additional data from our group suggests that E_2 regulates histone acetylation and *Bdnf* gene expression in a manner similar to young females [196]. On the other hand, systemic or intrahippocampal E_2 administered immediately post-training fails to enhance OR or activate dorsal hippocampal cell signaling in aged (20+ months of age) female

Table 5
Effects of exogenous estradiol and progesterone on object memory in middle-aged and aged female rodents.

Species	Age at testing	Type of hormone	ROA	Timing of administration[a]	Task(s)	Effect on OR and/or OP	Ref. no.	Reference
Estradiol								
Mouse	Middle-aged (16–17 months)	E_2	Systemic	Pre-training	OR	Chronic E_2 in drinking water (1000, 1500, 2500 nM) for 5 weeks before training enhanced OR	[211]	Fernandez and Frick (2004)
Rat	Middle-aged (11 and 17 months)	E_2	Systemic	Pre-training	OR	In mice OVXed at 7–9 weeks of age, E_2 enhanced OR when given via silastics for 9 or 15 months and via acute pre-training injection	[16]	Vedder et al. (2014)
Rat	Middle-aged (13 months)	CEE	Systemic	Post-training	OR	CEE (0.625 mg/kg) enhanced OR	[213]	Walf and Frye (2008)
Mouse	Middle-aged (17 months)	Water-soluble E_2	Systemic	Post-training	OR	E_2 (0.2 mg/kg) enhanced OR	[161]	Gresack et al. (2007)
Mouse	Middle-aged (17 months)	Water-soluble E_2	Intra-hippocampal	Post-training	OR	E_2 (5 μg) infused bilaterally into the dorsal hippocampus enhanced OR	[81]	Fan et al. (2010)
Mouse	Aged (21 months)	Water-soluble E_2	Systemic	Pre-training	OR	E_2 (0.2 mg/kg) injected every day or twice/week from 18 months through 21 months of age did not enhance OR	[214]	Gresack and Frick (2006)
Rat	Aged (20 months)	E_2	Systemic	Pre-training	OP	Chronic E_2 silastics implanted at 14 months enhanced OP tested at 20 months	[212]	Walf et al. (2009)
Rat	Aged (21 months)	E_2	Systemic	Pre-training	OR	In mice OVXed at 7–9 weeks of age, E_2 did not enhance OR when given via silastics for 19 months and via acute pre-training injection; however, acute E_2 enhanced OR in rats OVXed at 20 months and tested at 21 months	[16]	Vedder et al. (2014)
Mouse	Aged (22 months)	Water-soluble E_2	Systemic	Post-training	OR	E_2 (0.2 mg/kg) did not enhance OR	[162]	Gresack et al. (2007)
Mouse	Aged (22 months)	Water-soluble E_2	Systemic	Post-training	OR	E_2 (0.2 mg/kg) did not enhance OR	[161]	Gresack et al. (2007)
Mouse	Aged (21 months)	Water-soluble E_2	Intra-hippocampal	Post-training	OR	E_2 (5 μg) infused bilaterally into the dorsal hippocampus did not enhance OR	[81]	Fan et al. (2010)
Progesterone								
Mouse	Young middle-age (9 months)	P_4	Systemic	Pre-training	OR, OP	Chronic P_4 silastics implanted at 6 months enhanced OR and OP tested at 9 months	[236]	Frye and Walf (2008)
Mouse	Middle-aged (16 months)	Water-soluble P_4	Systemic	Post-training	OR	P_4 (10 or 20 mg/kg) enhanced OR tested 24 h, but not 48 h, after training	[131]	Lewis, Orr, and Frick (2008)
Mouse	Middle-aged/Aged (18–22 months)	P_4	Systemic	Post-training	OR	P_4 (10 mg/kg) enhanced OR in females and males	[226]	Frye and Walf (2008)
Mouse	Aged (20–24 months)	P_4	Systemic	Post-training	OP	P_4 (10 mg/kg) enhanced OP	[225]	Frye and Walf (2010)
Mouse	Aged (21 months)	Water-soluble P_4	Systemic	Post-training	OR	P_4 (10 mg/kg) enhanced OR tested 24 h after training; P_4 (5 or 10 mg/kg) enhanced OR tested 48 h after training	[131]	Lewis et al. (2008)

Note: ROA = route of administration; OR = object recognition; OP = object placement; OVXed = ovariectomized; CEE = conjugated equine estrogens.
[a] Post-training treatments were given immediately after training unless indicated otherwise in the "Effect on OR and/or OP" column.

mice [81,161,162,214], suggesting a loss of responsiveness to E_2 in old age. E_2 treatment has also proved unsuccessful in improving the performance of aged females in other types of hippocampal-dependent tasks, such as the radial arm maze [161,214], T-maze active avoidance [215], and spatial water maze [161,216]. This is not to say that the aged female brain cannot respond to E_2 under the right conditions, as there are many instances in which E_2 given chronically prior to training can improve memory in aged females (e.g., [16,95,217]). But whether E_2 enhances memory in aged females depends on numerous methodological issues as previously discussed [95]. Collectively, however, most studies indicate that the aged female brain exhibits a reduced level of responsiveness to ovarian hormones (Table 5), perhaps due to a reduction in the number and sensitivity of ERα and ERβ in the hippocampus that may compromise E_2's ability to signal through these receptors [218–220]. The behavioral findings support the existence of a critical period during early menopause in which estrogen replacement can effectively improve memory [221–224]. In the clinical literature, this "critical period hypothesis" suggests that initiating estrogen therapy during early menopause or middle age is essential to prevent or reduce cognitive decline [94,221,222]. The data from post-training treatments in OR support the existence of this critical period in rodents, and so this task could be instrumental in determining the neurobiological origins of the critical period, as well as to developing treatments to extend the critical period in aged women.

Few studies have examined the mnemonic effects of P_4 in middle-aged or aged rodents, but those that have generally report

beneficial effects. In middle-aged ovariectomized mice, chronic pre-training or acute post-training treatment with P_4 enhanced OR [131,226,236]. In addition, the P_4 metabolite 3α,5α-THP also significantly enhances OR memory in middle-aged female rats [210]. Similarly, in aged gonadally-intact or ovariectomized mice, post-training injection of P_4 significantly improved both OR and OP memory relative to vehicle-treated mice [131,225]. Interestingly, systemic P_4 treatment immediately after training facilitated OR memory consolidation in both middle-aged and aged female mice 24 h later, but only in aged mice 48 h later [131]. These data suggest that aged females may be more sensitive than middle-aged females to the memory-enhancing effects of P_4. Consistent with this notion, P_4 also improves the memory of aged female mice in other hippocampal-dependent memory tasks including T-maze, water maze, and contextual fear conditioning [226]. Such evidence that P_4, but not E_2, can reverse hippocampal memory deficits in aged rodents suggests that P_4 may regulate memory through mechanisms that differ or are less sensitive to aging than those used by E_2. Such differential sensitivity to E_2 and P_4 is worth exploring with respect to the development of future treatments to reduce memory decline in post-menopausal women.

9. Conclusions and future directions

E_2 and P_4 are important regulators of object recognition and spatial memory in rodents, as illustrated by their effects on memory in the OR and OP tasks. Our laboratory and others have made great strides in recent years using these tasks as tools to understand the extent to which E_2 and P_4 regulate hippocampal memory formation. We have begun to identify the essential receptors, cell-signaling pathways, and epigenetic processes necessary for E_2 and P_4 to enhance OR and OP, but we have considerably more work to do to identify the complex molecular mechanisms underlying hormonal regulation of object memory. Vital issues to address in future years include determining the extent to which rapid changes in cell signaling and epigenetics translate into structural alterations that maintain long-term memories, and defining the essential genes and gene products that support the synaptic plasticity underlying hormonal regulation of memory consolidation. As discussed above, many other key questions have yet to be resolved. For example, does ovarian function play a significant role in the response to hormone treatment? How do hormones regulate object memory during the estrous cycle, pregnancy, and reproductive senescence? Does progesterone regulate object memory itself via progesterone receptors or, rather, via its conversion to neurosteroid and/or sex steroid metabolites? How might the effects of clinically utilized hormone preparations on object memory differ from the E_2 and P_4 used in rodent studies? The answers to these questions would fundamentally advance our understanding of the key neural mechanisms through which E_2 and P_4 regulate memory formation, and provide sorely needed insight into the etiology and symptomatology of mental illnesses for which women are at increased risk, such as depression, anxiety disorders, schizophrenia, and dementia [227–230].

Along these lines, dysfunction in multiple cognitive brain regions is characteristic of several neuropsychiatric and neurodegenerative diseases that predominantly affect women (e.g., depression, anxiety disorders). Yet studies of hormonal regulation of object memory in rodents have focused largely on the hippocampus. Therefore, another important future direction is to identify the brain regions involved in hormonal modulation of OR and OP. The dorsal hippocampus is a key modulator for object-based memory tasks, as illustrated by the many examples presented above in which direct dorsal hippocampal infusions of hormones or other drugs altered memory consolidation in OR and OP. However, far too few studies have examined hormonal regulation in other brain regions that mediate OR and OP memory. One such study recently reported that E_2 infused into the perirhinal cortex/entorhinal cortex region enhanced OR memory in young ovariectomized rats [231]. Surely, other medial temporal lobe regions, as well as other cortical regions (e.g., prefrontal cortex) also play key roles. As such, we would encourage more studies examining hormonal regulation of other brain regions to gain a more complete understanding of how hormones regulate memory formation in the OR and OP tasks.

Another important area in which object memory tasks may prove useful is in understanding the etiology of sex differences in cognitive function. Women are significantly more likely than men to develop age-related memory decline, Alzheimer's disease, depression, anxiety, and mood disorders [224,227,228,232,233]. Further, for many of these disorders, women with lower endogenous levels of E_2 have exacerbated symptoms compared to women with higher levels of E_2 and men [218–220]. Yet why women are at increased risk for developing certain mental illnesses is unclear. Much of this uncertainty stems from the fact that many of the cellular and molecular mechanisms through which sex steroid hormones like E_2 and P_4 affect brain function remain unknown. As such, understanding the neural mechanisms through which E_2 and P_4 regulate memory function may shed light on sex differences in risk of mental illness. Few studies have examined sex differences in OR and OP, and these are somewhat contradictory. For example, our laboratory reported that male mice outperform female mice in two different OR tasks and an OP task [140]. However, others report a female advantage in OR under conditions of high E_2 and P_4 levels [234] or high object similarity [235]. As such, more research on sex differences in these tasks would help establish the parameters under which sex differences may be observed, and could provide insights into how sex differences contribute to increased susceptibility for developing certain mental illnesses.

In conclusion, this review has illustrated the importance of ovarian sex steroid hormones in regulating object memory. As should be clear from the discussion above, many questions remain to be answered to more fully understand how hormones regulate the various aspects of object memory. Significant progress in resolving these issues could allow researchers to identify putative drug targets that might lead to novel therapeutics for maintaining mental health in women. As such, it will be imperative to continue this work in future years, and we encourage researchers to consider the potential contributions of these hormones to their own experiments.

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