PACIFIC JOURNAL OF MEDICAL SCIENCES

{Formerly: Medical Sciences Bulletin}

ISSN: 2072 – 1625

Pac. J. Med. Sci. (PJMS)

www.pacjmedsci1625.com. Email: managingeditorpjms1625@gmail.com.

A REVIEW:

BEYOND REPRODUCTION: A COMPREHENSIVE REVIEW OF ESTROGENIC ACTIONS IN THE MAMMALIAN BRAIN

Running title: Role of estrogens in the brain

^Wahab I. Abdulmajeed*, Sekinat F. Yusuf*, Mary O. Dada*, Maleek O. Oyedele*, Nuriyat O. Oseni*, Christianah B. Oyakojo, Musa O. Habeebullah*, Maryam T. Ayinla*, Lawrence A. Olatunji***

*Department of Physiology, Faculty of Basic Medical Sciences, University of Ilorin, Ilorin, Nigeria.
**Department of Physiology, Faculty of Basic Medical Sciences, Federal University of Technology, Akure, Nigeria.

^Correspondence: abdulmajeed.w@unilorin.edu.ng

Submitted: January 2026. Accepted: March 2026

A REVIEW:

BEYOND REPRODUCTION: A COMPREHENSIVE REVIEW OF ESTROGENIC ACTIONS IN THE MAMMALIAN BRAIN

Running title: Role of estrogens in the brain

^Wahab I. Abdulmajeed*, Sekinat F. Yusuf*, Mary O. Dada*, Maleek O. Oyedele*, Nuriyat O. Oseni*, Christianah B. Oyakojo, Musa O. Habeebullah*, Maryam T. Ayinla*, Lawrence A. Olatunji***

*Department of Physiology, Faculty of Basic Medical Sciences, University of Ilorin, Ilorin, Nigeria.
**Department of Physiology, Faculty of Basic Medical Sciences, Federal University of Technology, Akure, Nigeria.

^Correspondence: abdulmajeed.w@unilorin.edu.ng

Submitted: January 2026. Accepted: March 2026

ABSTRACT
For decades, estrogens have been regarded as reproductive hormones. However, research in the last few years has altered this perspective. It has been shown that estrogen signaling plays a widespread and crucial role in regulating brain function throughout life in both men and women. This review summarizes recent studies from 2005 to 2025 on how estrogens work in the brain, including their mechanisms, targets, and effects. We outline where nuclear estrogen receptors (ERα, ERβ) and membrane-associated receptors (like GPER1) are found in the brain. We also highlight their roles in synaptic plasticity, adult neurogenesis, inflammation and energy use. We examine the protective and cognitive benefits of estrogens, particularly regarding neurodegenerative diseases like Alzheimer's, psychiatric issues such as depression, and brain injuries. We emphasize the importance of timing, dosage, and hormonal context within the "window of opportunity" or "critical period" hypothesis. Recent updates to hormone replacement therapy (HRT) guidelines highlight the brain health benefits of starting treatment early. Finally, we address challenges and future directions, including the development of brain-selective estrogen receptor modulators (SERMs) and tailored approaches that account for sex differences and genetic factors. The evidence clearly shows that estrogens are powerful neuroactive steroids that are vital for brain health and resilience.

Keywords: estrogen, estradiol, estrogen receptors, neuroprotection, synaptic plasticity, neurogenesis, cognition, menopause, Alzheimer's disease.

Methods: This review was conducted by systematically searching PubMed, Scopus, and Google Scholar databases using keywords such as "estrogen brain," "neuro-estrogen," "estrogen receptors," "neuroprotection," "synaptic plasticity," "neurogenesis," "cognition," "menopause," and "Alzheimer's disease." We focused primarily on peer-reviewed articles published between 2005 and 2025. Studies involving cellular, animal, and human models that discussed how estrogens work in the brain were included. We excluded non-English publications and studies that lacked rigorous methods. More than 150 articles were screened, and 63 were selected for review. We critically evaluated the data for consistency, quality, and relevance, with special attention to recent advances to fill gaps in earlier research.

INTRODUCTION

Estrogens, especially 17β-estradiol (E2), have been traditionally defined as steroid hormones that control the development and function of the female reproductive system. The discovery of estrogen receptors (ERs) in various brain regions outside the usual hormonal control areas, like the hippocampus and prefrontal cortex, has revealed a much broader role for these hormones [1]. The last two decades have seen a surge of research in this area, driven by advancements in molecular and genetic tools, the recognition of significant differences between sexes in neurological and psychiatric disorders [2] and increased interest in women's brain health during menopause.

This wave of research has transformed our understanding of estrogens from being solely reproductive signals to recognizing them as essential neuroactive steroids that significantly influence brain structure and function throughout life for both males and females [3]. Estrogens can affect synaptic plasticity, mood, energy metabolism, provide neuroprotective effects, and support cognitive processes such as learning and memory [4]. Estrogens have been shown to modulate neuroinflammation via pathways such as PI3K/Akt and NF-κB, with important implications for aging and neurodegeneration [5-7]. This review aims to consolidate and evaluate key findings from peer-reviewed literature published between 2005 and 2025. By synthesizing evidence from cellular, animal, and human studies, the article will show that estrogen actions are crucial for brain development, balance, and resilience, affecting our understanding and treatment of various brain disorders.

Estrogen Synthesis and Receptor Systems in the Brain

Central Synthesis: The Critical Role of Neuroestrogen.

A groundbreaking discovery in the last twenty years is that the brain can produce estrogen. Neurons, astrocytes, and, to a lesser extent, microglia have the enzyme aromatase (CYP19A1), which converts testosterone into 17β-estradiol (E2) [8,9]. This local production, called "neuroestrogen," enables rapid, paracrine, sex-independent regulation of brain function. The control of aromatase in the brain differs from that in other tissues; it often increases in response to neural injury or synaptic activity, suggesting a role in neuroprotection and plasticity [10].

Neuroestrogen is important in its functional implications. E2 produced by the brain in males due to circulating testosterone is crucial in sexual differentiation and neural development of the brain, as well as adult cognitive ability [11].

Treatment with aromatase inhibitors results in impairment in spatial memory, synaptic plasticity, and male sexual behavior in rodents [12]. In females, local synthesis may help to adjust neural circuits during fluctuations in ovarian hormones across the menstrual cycle and throughout life. Research in songbirds, where neuroestrogen plays a clear role in learning and producing seasonal songs, has offered valuable insights into its mechanisms [13]. Experiments in mammals using neuron-specific aromatase knockout (ArKO) models have demonstrated that neuroestrogen is essential for synaptic plasticity, neurogenesis, and memory consolidation in the hippocampus [14,15]. Also, studies have highlighted sex differences in neuroestrogen synthesis. Males have higher aromatase levels in specific brain areas, influencing their behavior [16]

Estrogen Receptor Diversity and Signaling Mechanisms:

Nuclear Receptors (Classical Genomic Signaling): ERα and ERβ are transcription factors activated by E2 that belong to the nuclear receptor superfamily. The binding of E2 in the cytoplasm causes a conformational change and moves to the nucleus, where it attaches to specific DNA sequences called Estrogen Response Elements (EREs). This process regulates the transcription of target genes over hours to days [17]. They can also have "non-classical" effects by interacting with other transcription factors (e.g., AP-1, NF-κB, CREB) without directly binding on DNA. ERβ is particularly abundant in regions like the cortex, hippocampus, and serotonergic neurons, linking it to cognition, mood, and neuroprotection [18]. While ERα is present in these areas, its role is more prominent in hypothalamic regions that control reproductive behaviors.

Membrane-Associated Receptors and Rapid Non-Genomic Signaling:

A key advancement in the field has been identifying rapid estrogen effects (within seconds to minutes) on kinase activity, calcium movement, and synaptic strengthening. These effects come from receptors located at the plasma membrane or associated with membrane areas like caveolae.

GPER1 (GPER, GPR30):

Discovered in 2005, GPER1 is a seven-transmembrane G-protein-coupled receptor that binds E2 with high affinity [19]. It is found throughout neurons and glia in the brain. When activated, it quickly causes intracellular calcium changes and activates essential neuroprotective signaling pathways like PI3K/Akt and MAPK/ERK [20]. GPER1 is recognized as a major mediator of estrogen's rapid effects on synaptic plasticity, neuroprotection, and behavior [21]. GPER1 is known to be involved in cognitive functions, neuroinflammation and psychiatric disorders, showing promise for therapeutic uses [19].

Membrane-Initiated Steroid Signaling (MISS): Some classical ERα and ERβ can be modified to help them move to the plasma membrane [22]. These localized ERs interact with metabotropic glutamate receptors and other proteins to activate similar secondary messenger pathways (e.g., Src/ERK, PI3K) as GPER1. The MISS pathway is crucial for the rapid formation of dendritic spines in the hippocampus [23].

Estrogen-Related Receptors (ERRs):

The orphan receptors ERRα, ERRβ, and ERRγ share similarities with ERs but do not bind natural estrogens. They are highly expressed in metabolically active tissues, including the brain, where they act as transcription factors that regulate genes involved in creating energy and metabolism [24]. Their interaction with coactivators like PGC-1α positions them as significant regulators of neuronal energy use, which is increasingly tied to the neuroprotective effects of estrogen [25].

This complex array of receptors and signaling mechanisms enables estrogens to modulate brain functions, from the quick adjustments of synaptic activity to guiding long-term changes in gene expression that reshape neuronal structure and resilience.

Fundamental Neurobiological Processes that are under the control of Estrogens:

Synaptic Plasticity and Spine Dynamics

Estrogen consistently boosts strength and lowers the threshold for LTP in the CA1 region of the hippocampus [26]. This effect involves a coordinated mechanism. Rapid signaling through mERα/β or GPER1 enhances NMDA receptor activity and increases the surface expression of AMPA receptors, specifically GluA1 subunits, which improves the responsiveness of the postsynaptic neurons [27, 28]. At the same time, genomic actions via nuclear ERs lead to an increase in the transcription of NMDA receptor subunits (GluN1, GluN2B), synaptic scaffolding proteins like PSD-95, and proteins involved in spine formation [29].

Furthermore, a striking finding is that E2 can cause a rapid (within 30-120 minutes) and significant (30 - 50%) increase in dendritic spine density on CA1 pyramidal neuron apical dendrites [30,31]. This effect is robust and linked to fluctuations during the estrous cycle in rodents. The molecular cascade involves ER membrane activation of the Rho GTPase/Rho kinase/LIM-kinase pathway, which inactivates the actin-depolymerizing protein cofilin, leading to rapid actin polymerization and spine formation [32]. Additionally, E2 activates local dendritic protein synthesis through the mTOR and ERK pathways, providing the necessary components for new synapses [33].

Also, estrogens finely adjust the E/I balance within neural circuits. They can reduce inhibitory tone by lowering glutamic acid decarboxylase (GAD67) expression in specific interneurons

[34]. and by altering the composition of GABA receptor subunits. At the same time, they enhance excitatory activity by increasing NMDAR activity. This shift decreases inhibition while increasing excitation, creating a neural network state that is very conducive to plasticity and information processing [35].

Adult Neurogenesis:

The hippocampus can produce new neurons throughout life, in a process known as adult neurogenesis. Estrogens are important positive regulators of this process in the sub-granular zone of the dentate gyrus, with recent evidence showing age- and sex-specific modulation. Systemic or intrahippocampal administration of E2 increases the proliferation of neural progenitor cells and improves the survival of newly formed neurons [36,37]. This effect mainly occurs through ERα and ERβ, which are found on progenitor cells. E2 signaling promotes cell cycle progression and prevents cell death through the activation of survival pathways, such as PI3K/Akt [38]. Beyond increasing cell numbers, E2 supports the maturation and functional integration of new neurons into existing hippocampal circuits. It speeds up dendritic branching and the expression of mature neuronal markers [39]. This process is essential for certain types of memory that rely on the hippocampus, especially for distinguishing between similar experiences [40]. The drop in circulating E2 levels during menopause and aging is linked to a marked decline in markers of adult neurogenesis in animal models [41]. Exogenous administration of E2 in these models can reverse this decline. This suggests a direct relationship between hormonal loss and reduced neural flexibility in aging [6]. While measuring neurogenesis in living humans is still challenging, this connection provides insights into cognitive changes related to menopause.

Neuroprotection, Anti-Inflammation and Bioenergetics:

Estrogen is a potent inhibitor of cell death. It activates the PI3K/Akt and MAPK/ERK survival pathways, which leads to the phosphorylation and inactivation of pro-apoptotic factors like Bad and caspase-9, while increasing the expression of anti-apoptotic proteins such as Bcl-2 and Bcl-xL [42]. This mechanism is critical in stroke models, traumatic brain injuries, and neurodegenerative diseases. E2 and its non-feminizing metabolites (e.g., 2-hydroxyestradiol, 2-methoxyestradiol) have inherent antioxidant properties. The phenolic A-ring of estradiol can directly neutralize reactive oxygen species (ROS) and lipid peroxides [43]. Furthermore, E2 increases the expression and activity of natural antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase, and catalase, which strengthens the brain's defense against oxidative stress, an important factor in aging and neurodegeneration [44].

Similarly, when microglia and astrocytes, which serve as the immune cells in the brain, are activated, they release pro-inflammatory cytokines (TNF-α, IL-1β, IL-6), chemokines, and neurotoxic factors. Estrogens primarily act through ERα and GPER1 to exert significant anti-inflammatory effects. They suppress microglial activation, stop the nuclear translocation of NF-κB (a major regulator of inflammation), and encourage a shift towards a protective, anti-inflammatory state in microglia [45,46]. These actions are particularly relevant to Alzheimer's disease, Parkinson's disease, and multiple sclerosis, which all involve significant neuroinflammation.

Neurons are highly demanding on metabolism. Estrogens help maintain neuronal energy levels by improving mitochondrial function. They boost mitochondrial respiration, ATP production, and the expression of components in the mitochondrial electron transport chain [47]. E2 also enhances glucose transport into neurons and astrocytes by increasing glucose transporters (GLUTs) and boosts aerobic glycolysis [48]. By ensuring that neurons have the energy capacity to meet demand and resist stress, estrogen signaling is a vital part of neural resilience.

Summarily, this review synthesizes emerging evidence that estrogens, besides their reproductive roles, are important neuroactive steroids that regulate synaptic plasticity, adult neurogenesis, inflammation and energy use in both sexes. In the same vein, the benefits of estrogens, which depend on timing and dosage, are critical determinants of their neuroprotective efficacy in brain injuries, psychiatric disorders and Alzheimer's diseases. While some challenges have been addressed, the development of brain-selective estrogen receptor modulators (SERMs) holds a promising future direction in addressing genetic and gender differences in treatment response.

Functional Outcomes and Translational Implications:

Cognition and Memory

There is strong clinical and preclinical evidence that supports the critical (though complicated) effect of estrogens on memory, which relies on the hippocampus and prefrontal cortex. For instance, the performance of the verbal memory and executive function tasks during the follicular phase among healthy premenopausal women is positively related to the endogenous levels of E2, and this phenomenon reflects less cognitive dysfunction [49]. Bilateral ovariectomy in the absence of estrogen treatment is equally linked with faster brain aging and the two-fold risk of impaired cognitive ability or dementia in old age. Such risks are mitigated with estrogen replacement that starts at the surgical menopause [50].

The Women’s Health Initiative Memory Study (WHIMS) contributed greatly to the study of the effects of Estrogen on cognition. The study established that women between 65 and 79 years who initiated oral conjugated equine estrogens (CEE) with or without medroxyprogesterone acetate (MPA) were at increased risk of experiencing dementia and mild impaired thinking [51]. This unexpected finding, even with a large body of preclinical neuroprotection evidence, prompted the formulation of the "window of opportunity/critical period" hypothesis [52,53]. The hypothesis is that brain functioning and maintenance can be defended by estrogen therapy at perimenopause or early postmenopause, before age 60 or within 5-10 years of menopause. Late treatment initiation when extensive age- or disease-induced changes in the brain, such as increased Ab deposition or cerebrovascular complication may exist, may be both ineffective and even detrimental. Animal experiments support this timeline, with estrogen protection following ovariectomy being more effective in middle-aged rats than in those treated later [54]. According to the Kronos Early Estrogen Prevention Study (KEEPS), early initiation of transdermal estrogen (at early menopause) could have a beneficial impact on cognitive outcomes [55]. Recent changes to the hormone replacement treatment (HRT) have suggested that hormone replacement should be initiated during the period age 10 years after menopause or prior to age 60 to achieve maximum cognitive advantages as well as have black-box warnings on timing removed.

Affective and Neuropsychiatric Disorders

Depression:

High E2 variations or declines are associated with high risks of depressive episodes in vulnerable women such as during the postpartum, perimenopausal, and premenstrual phases [56]. Mechanistically, E2 promotes serotonergic activity by increasing tryptophan hydroxylase production, the rate-limiting enzyme in 5-HT synthesis, regulation of 5-HT1A and 5-HT2A receptor expression and activity and decreasing the activity of monoamine oxidase, which breaks down monoamines [57]. Transdermal E2 has good monotherapy in PMD as well as adjunctive therapy [58], and the neuroprotective effect of estrogen has infinite opportunities to stimulate brain health, resilience, and cognitive longevity across the life span in both genders.

Schizophrenia:

Epidemiological studies indicate that sex disparity in schizophrenia is large. The diseases of women are less severe in nature but more emotionally severe, late onset and second peak incidence after 45. Gogos reported that the symptoms tend to be more severe when estrogen levels are low, after giving birth, and around the menstrual cycle [59]. It is considered that estrogen may protect by improving the efficiency of prefrontal cortex and regulating dopamine, resulting in a reduction of striatal hyper-dopaminergia. Some randomized controlled trials have found that adjuvant transdermal estradiol or selective estrogen receptor modulators, including raloxibine, can reduce positive and negative symptoms in women with schizophrenia when used in conjunction with regular antipsychotic medication [60].

Neurodegenerative Diseases Alzheimer's Disease (AD):

Estrogens affect all the key pathogenic characteristics of AD. They stimulate the non-amyloidogenic cleavage of amyloid precursor protein (APP) via a-secretase pathway (ADAM10), thereby reducing the production of neurotoxic amyloid-β peptides [61]. They inhibit the hyperphosphorylation of tau that causes the development of neurofibrillary tangles by blocking the action of kinases like GSK-3β [62]. They also help with mitochondrial functionality and synaptic stability, as well as decreasing neuroinflammation. One of the biological risk factors of AD is E2 depletion, which is seen in the substantially higher rates of AD prevalence among postmenopausal women, despite the longer lifespan of females [63]. This is most evident in the critical period hypothesis, which is why the trials of hormone therapy in older women with probable AD have failed, though observational studies of early-initiating women have demonstrated a reduction of risk.

CONCLUSION

Within the past two decades, research has shown that the range of estrogen activity in the brain is significantly wider than reproductive neuroendocrinology. Initially, estrogens were not complex; however, various pleiotropic modulators participated in the activities of synaptic plasticity, cellular resilience, neuroimmune mechanisms, and energy homeostasis. These caused a complex program of genomic and non-genomic signaling that enhanced cognitive processes, buffered affective disorders, and highly secured the central nervous system against various insults. It is one of the enormous tasks of our reality to safely, effectively, and feasibly translate these convincing preclinical results into clinical therapy of neurodegenerative diseases, psychiatric disorders, and brain injury. This receptor-specific knowledge of the effects of estrogen and their relative significance and further development of new neural-targeted ligands offers a viable and rational future path. In fact, there is no better way of ensuring that the brain can expect health, resistance, and cognitive longevity, particularly among women and men of all age groups, than to harness this potent endogenous neuroprotective system.

Acknowledgement:

The authors wish to thank members of Dr. Abdulmajeed's project group for their comments on the early version of the manuscript.

Conflict of interest: None

REFERENCES

1. McEwen, B. S., & Milner, T. A. (2017). Understanding the broad influence of sex hormones and sex differences in the brain. Journal of Neuroscience Research, 95(1-2), 24-39.
2. Gillies, G. E., & McArthur, S. (2010). Estrogen actions in the brain and the basis for differential

action in men and women: a case for sex-specific medicines. Pharmacological Reviews, 62(2), 155-198.

3. Brinton, R. D. (2009). Estrogen-induced plasticity from cells to circuits: predictions for cognitive function. Trends in Pharmacological Sciences, 30(4), 212-222.
4. Frick, K. M. (2015). Molecular mechanisms underlying the memory-enhancing effects of estradiol. Hormones and Behavior, 74, 4-18.
5. Bai, N., Zhang, Q., Zhang, W., Liu, B., Yang, F., Brann, D., & Wang, R. (2020) G-protein-coupled estrogen receptor activation upregulates interleukin-1 receptor antagonist in the hippocampus after global cerebral ischemia: implications for neuronal self-defense. Journal Neuroinflammation, 17(1):45.
6. Huang, Y., Sun, W., Gao, F., Ma, H., Yuan, T., Liu, Z., Liu, H., Hu, J., Bai, J., Zhang, X. & Wang R. (2023). Brain-Derived Estrogen Regulates Neurogenesis, Learning and Memory with Aging in Female Rats. Biology, 12(6), 760.
7. Lu, J., Xian, T.J., Li, C.J., & Wang, Y. (2025). The estrogen–brain interface in neuroinflammation: a multidimensional mechanistic insight. Frontiers in Aging Neuroscience, 17, 1671552.
8. Hojo, Y., Hattori, T.A., Enami, T., Furukawa, A., Suzuki, K., Ishii, H.T., Mukai, H., Morrison, J.H., Janssen, W.G., Kominami, S., Harada, N., Kimoto, T., Kawato, S. (2004). Adult male rat hippocampus synthesizes estradiol from pregnenolone by cytochromes P45017alpha and P450 aromatase localized in neurons. Proc Natl Acad Sci U S A., 101(3):865-70.
9. Azcoitia, I., Yague, J. G., & Garcia-Segura, L. M. (2011). Estradiol synthesis within the human brain. Neuroscience, 191, 139-147.
10. Saldanha, C. J., Duncan, K. A., & Walters, B. J. (2009). Neuroprotective actions of brain aromatase. Frontiers in Neuroendocrinology, 30(2), 106-118.
11. Roselli, C. E., Liu, M., & Hurn, P. D. (2009). Brain aromatization: classic roles and new perspectives. Seminars in Reproductive Medicine, 27(3), 207-217.
12. Vierk, R., Glassmeier, G., Zhou, L., Brandt, N., Fester, L., Dudzinski, D., Wilkars, W., Bender, R.A., Lewerenz, M., Gloger, S., Graser, L., Schwarz, J. & Rune, G.M. (2012). Aromatase inhibition abolishes LTP generation in female but not in male mice. Journal Neurosci., 32(24): 8116 - 8126.
13. Remage-Healey, L., Maidment, N. T., & Schlinger, B. A. (2008). Forebrain steroid levels fluctuate rapidly during social interactions. Nature Neuroscience, 11(11), 1327-1334.
14. Zhou, L., Fester, L., von Blittersdorff, B., Hassu, B., Nogens, H., Prange-Kiel, J., & Rune, G. M. (2010). Aromatase inhibitors induce spine synapse loss in the hippocampus of ovariectomized mice. Endocrinology, 151 (3), 1153-1160.
15. Fester, L., Prange-Kiel, J., Jarry, H., & Rune, G. M. (2011). Estrogen synthesis in the hippocampus. Cell and Tissue Research, 345(3), 285-294.
16. Immenschuh, J., Thalhammer, S.B., Sundström-Poromaa, I., Biegon, Dumas, S., & Comasco, E. (2023). Sex differences in distribution and identity of aromatase gene expressing cells in the young adult rat brain. Biology of Sex Differences, 14 (1), 54.
17. Heldring, N., Pike, A., Andersson, S., Matthews, J., Cheng, G., Hartman, J., Tujague, M., Ström, A., Treuter, E., Warner, M. & Gustafsson, J.A. (2007). Estrogen receptors: how do they signal and what are their targets. Physiology Rev; 87(3): 905-31.
18. Mitra, S.W., Hoskin, E., Yudkovitz, J., Pear, L., Wilkinson, H.A., Hayashi, S., Pfaff, D.W., Ogawa, S., Rohrer, S.P., Schaeffer, J.M., McEwen, B.S, Alves, S.E. (2003). Immunolocalization of estrogen receptor beta in the mouse brain: comparison with estrogen receptor alpha. Endocrinology; 144(5):2055-67.
19. Prossnitz, E. R., & Barton, M. (2023). The G-protein-coupled estrogen receptor GPER in health and disease. Nature Reviews Endocrinology, 19(7), 407-424.
20. Gingerich, S., Kim, G. L., Chalmers, J. A., Koletar, M. M., Wang, X., & Belsham, D. D. (2010). Estrogen receptor α and G-protein coupled receptor 30 mediate the neuroprotective effects of 17β-estradiol in novel murine hippocampal cell models. Neuroscience, 170(1), 54-66.
21. Boulware, M. I., Weick, J. P., Becklund, B. R., Kuo, S. P., Groth, R. D., & Mermelstein, P. G. (2005). Estradiol activates group I and II metabotropic glutamate receptor signaling, leading to opposing influences on cAMP response element-binding protein. Journal of Neuroscience, 25(20), 5066-5078.
22. Levin, E. R. (2009). Plasma membrane estrogen receptors. Trends in Endocrinology & Metabolism, 20(10), 477-482.
23. Srivastava, D. P., Waters, E. M., Mermelstein, P. G., Kramár, E. A., Shors, T. J., & Liu, F. (2011). Rapid estrogen signaling in the brain: implications for the fine-tuning of neuronal circuitry. Journal of Neuroscience, 31(45), 16056-16063.
24. Giguère, V. (2008). Transcriptional control of energy homeostasis by the estrogen-related receptors. Endocrine Reviews, 29(6), 677-696.
25. Brinton, R. D. (2008). The healthy cell bias of estrogen action: mitochondrial bioenergetics and neurological implications. Trends in Neurosciences, 31(10), 529-537.

26. Foy, M. R., Baudry, M., Foy, J. G., & Thompson, R. F. (2008). 17β-estradiol modifies stress-induced and age-related changes in hippocampal synaptic plasticity. Behavioral Neuroscience, 122(2), 301.
27. Smith, C. C., & McMahon, L. L. (2006). Estradiol-induced increase in the magnitude of long-term potentiation is prevented by blocking NR2B-containing receptors. Journal of Neuroscience, 26(33), 8517-8522.
28. Oberlander, J. G., & Woolley, C. S. (2016). 17β-Estradiol acutely potentiates glutamatergic synaptic transmission in the hippocampus through distinct mechanisms in males and females. J of Neuroscience, 36 (9), 2677-2690.
29. Spencer, J. L., Waters, E. M., Romeo, R. D., Wood, G. E., Milner, T. A., & McEwen, B. S. (2008). Uncovering mechanisms of estrogen effects on hippocampal function. Frontiers in Neuroendocrinology, 29 (2), 219-237.
30. Woolley, C. S., & McEwen, B. S. (1993). Roles of estradiol and progesterone in regulation of hippocampal dendritic spine density during the estrous cycle in the rat. Journal of Comparative Neurology, 336(2), 293-306.
31. Srivastava, D. P., Woolfrey, K. M., Jones, K. A., Shum, C. Y., Lash, L. L., Swanson, G. T., & Penzes, P. (2008). Rapid enhancement of two-step wiring plasticity by estrogen and NMDA receptor activity. Proceedings of the National Academy of Sciences, 105(38), 14650-14655.
32. Waters, E.M., Yildirim, M., Janssen, W.G.M., Lou, W.Y.W., McEwen, B.S., Morrison, J.H., Milner, T.A. (2008). Estrogen and aging affect the synaptic distribution of estrogen receptor beta-immunoreactivity in the CA1 region of female rat hippocampus. Brain Research, 1236, 30-39.
33. Briz, V., & Baudry, M. (2014). Estrogen regulates protein synthesis and actin polymerization in hippocampal neurons through different molecular mechanisms. Frontiers in Endocrinology, 5, 22.
34. Rudick, C. N., & Woolley, C. S. (2001). Estrogen regulates functional inhibition of hippocampal CA1 pyramidal cells in the adult female rat. Journal of Neuroscience, 21(17), 6532-6543.
35. Smejkalova, T., & Woolley, C. S. (2010). Estradiol acutely potentiates hippocampal excitatory synaptic transmission through a presynaptic mechanism. Journal of Neuroscience, 30(48), 16137-16148.
36. Tanapat, P., Hastings, N. B., Reeves, A. J., & Gould, E. (1999). Estrogen stimulates a transient increase in the number of new neurons in the dentate gyrus of the adult female rat. Journal of Neuroscience, 19(14), 5792-5801.
37. Galea, L. A., Wainwright, S. R., Roes, M. M., Duarte-Guterman, P., Chow, C., & Hamson, D. K. (2013). Sex, hormones and neurogenesis in the hippocampus: hormonal modulation of neurogenesis and potential functional implications. Journal of Neuroendocrinology, 25(11), 1039-1061.
38. Won, C.K., Ha, S.J., Noh, H.S., Kang, S.S., Cho, G.J., Choi, W.S. & Koh, P.O. (2005). Estradiol prevents the injury-induced decrease of Akt activation and Bad phosphorylation in the hippocampus. Journal of Neuroscience Research, 88(8), 1775-1784.
39. Liu, F., Day, M., Muñiz, L.C., Bitran, D., Arias, R., Revilla-Sanchez, R., Grauer, S., Zhang, G., Kelley, C., Pulito, V., Sung, A., Mervis, R.F., Navarra, R., Hirst, W.D., Reinhart, P.H., Marquis, K.L., Moss, S.J., Pangalos, M.N., Brandon, N.J. (2008). Activation of estrogen receptor-beta regulates hippocampal synaptic plasticity and improves memory. Nat Neurosci. 11(3):334-43.
40. Toni, N., Laplagne, D. A., Zhao, C., Lombardi, G., Ribak, C. E., Gage, F. H., & Schinder, A. F. (2008). Neurons born in the adult dentate gyrus form functional synapses with target cells. Nature Neuroscience, 11(8), 901-907.
41. Barker, J. M., & Galea, L. A. (2008). Repeated estradiol administration alters different aspects of neurogenesis and cell death in the hippocampus of female, but not male, rats. Neuroscience, 152(4), 888-902.
42. Singh, M., Sétáló Jr, G., Guan, X., Frail, D. E., & Toran-Allerand, C. D. (1999). Estrogen-induced activation of mitogen-activated protein kinase in cerebral cortical explants: convergence of estrogen and neurotrophin signaling pathways. Journal of Neuroscience, 19(4), 1179-1188.
43. Behl, C., Skutella, T., Lezoualc'h, F., Post, A., Widmann, M., Newton, C. J., & Holsboer, F. (1997). Neuroprotection against oxidative stress by estrogens: structure-activity relationship. Molecular Pharmacology, 51(4), 535-541.
44. Borrás, C., Gambini, J., López-Grueso, R., Pallardó, F. V., & Viña, J. (2009). Direct antioxidant and protective effect of estradiol on isolated mitochondria. *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease, 1802 (1), 205-211.
45. Sárvári M., Kalló, I., Hrabovszky, E., Solymosi, N., Tóth, K., Likó, I., Molnár, B., Tihanyi, K., Liposits, Z. (2010) Estradiol replacement alters expression of genes related to neurotransmission and immune surveillance in the frontal cortex of middle-aged, ovariectomized rats. Endocrinology; 151 (8): 3847-62.
46. Vegeto, E., Benedusi, V., & Maggi, A. (2008). Estrogen anti-inflammatory activity in brain: a therapeutic opportunity for menopause and

neurodegenerative diseases. Frontiers in Neuroendocrinology, 29(4), 507-519.
47. Irwin, R. W., Yao, J., Hamilton, R. T., Cadenas, E., Brinton, R. D., & Nilsen, J. (2008). Progesterone and estrogen regulate oxidative metabolism in brain mitochondria. Endocrinology, 152(7), 2770-2781.
48. Rettberg, J. R., Yao, J., & Brinton, R. D. (2013). Estrogen: a master regulator of bioenergetic systems in the brain and body. Frontiers in Neuroendocrinology, 35(1), 8-30.
49. Rosenberg, L., & Park, S. (2002). Verbal and spatial functions across the menstrual cycle in healthy young women. Psychoneuroendocrinology, 27(7), 835-841.
50. Rocca, W. A., Bower, J. H., Maraganore, D. M., Ahlskog, J. E., Grossardt, B. R., De Andrade, M., & Melton III, L. J. (2007). Increased risk of cognitive impairment or dementia in women who underwent oophorectomy before menopause. Neurology, 69(11), 1074-1083.
51. Shumaker, S.A., Legault, C., Kuller, L., Rapp, S.R., Thal, L., Lane, D.S., Fillit, H., Stefanick, M.L., Hendrix, S.L., Lewis, C.E., Masaki, K., Coker, L.H. (2004). Women's Health Initiative Memory Study. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. JAMA, 291(24):2947-58
52. Brinton, R. D. (2005). Investigative models for determining hormone therapy-induced outcomes in brain: evidence in support of a healthy cell bias of estrogen action. Annals of the NY Academy of Sciences, 1052(1), 57-74.
53. Maki, P. M. (2006). Hormone therapy and cognitive function: is there a critical period for benefit? Neuroscience, 138(3), 1027-1030.
54. Daniel, J. M., Hulst, J. L., & Berbling, J. L. (2005). Estradiol replacement enhances working memory in middle-aged rats when initiated immediately after ovariectomy but not after a long-term period of ovarian hormone deprivation. Endocrinology, 147(1), 607-614.
55. Gleason, C.E., Dowling, N.M., Wharton, W., Manson, J.E., Miller, V.M., Atwood, C.S., Brinton, E.A., Cedars, M.I., Lobo, R.A., Merriam, G.R., Neal-Perry, G., Santoro, N.F., Taylor, H.S., Black, D.M., Budoff, M.J., Hodis H.N., Naftolin, F., Harman, S.M. & Asthana S. (2015). Effects of Hormone Therapy on Cognition and Mood in Recently Postmenopausal Women: Findings from the Randomized, Controlled KEEPS-Cognitive and Affective Study. PLoS Med.,12(6):e1001833.
56. Soares, C. N., & Zitek, B. (2008). Reproductive hormone sensitivity and risk for depression across the female life cycle: a continuum of vulnerability? Journal of Psychiatry & Neuroscience, 33(4), 331 - 343.
57. Bethea, C. L., Lu, N. Z., Gundlah, C., & Streicher, J. M. (2002). Diverse actions of ovarian steroids in the serotonin neural system. Frontiers in Neuroendocrinology, 23(1), 41-100.
58. Schmidt, P.J., Ben Dor, R., Martinez, P.E., Guerrieri, G.M., Harsh, V.L., Thompson, K., Koziol, D.E., Nieman, L.K. & Rubinow, D.R. (2015). Effects of estradiol withdrawal on mood in women with past perimenopausal depression: A randomized clinical trial. JAMA Psychiatry; 72(7):714-26.
59. Gogos, A., Ney, L. J., Seymour, N., Van Rheenen, T. E., & Felmingham, K. L. (2019). Sex differences in schizophrenia, bipolar disorder, and post-traumatic stress disorder: are gonadal hormones the link? British Journal of Pharmacology, 176(2), 4199-4135.
60. Kulkarni, J., Gavrilidis, E., Worsley, R., Van Rheenen T & Hayes, E. (2013). The role of estrogen in the treatment of men with schizophrenia. International Journal of Endocrinology and Metabolism, 11(13): 129 – 136.
61. Zhao, L., Yao, J., Mao, Z., Chen, S., Wang, Y., & Brinton, R. D. (2010). 17β-Estradiol regulates insulin-degrading enzyme expression via an ERβ/PI3-K pathway in hippocampus: relevance to Alzheimer's prevention. Neurobiology of Aging, 32(11), 1949-1963.
62. Yune, T.Y., Park, H.G., Lee, J.Y., & Oh, T.H. (2005). Estrogen-induced Bcl-2 expression after spinal cord injury is mediated through phosphoinositide-3-kinase-dependent phosphorylation of Bad. Journal of Neurotrauma, 25(9), 1121-1131.
63. Snyder, H.M., Asthana, S., Bain, L., Brinton, R., Craft, S., Dubal, D.B., Espeland, M.A., Gatz, M., Mielke, M.M., Raber, J., Rapp, P.R., Yaffe, K., & Carrillo, M.C. (2016). Sex biology contributions to vulnerability to Alzheimer's disease: A think tank convened by the Women's Alzheimer's Research Initiative. Alzheimers Dement., 12(11):1186-1196.