Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Behavioral Sciences

The middle-aged brain: biological sex and sex hormones shape memory circuitry

Emily G Jacobs[1,2] and Jill M Goldstein[3,4,5]

Over the last quarter century, a staggering number of brain imaging studies have probed the neural basis of age-related cognitive decline. Using multimodal brain imaging tools, we now have a clearer understanding of the morphological, neurochemical, and neurophysiological changes that accompany age-related declines in working memory, selective attention, inhibitory control, episodic memory and more. These studies generally target adults over the age of 65, a historical precedent rooted in the average retirement age of U.S. wage-earners. An unintended consequence of this adopted standard is that it overlooks one of the most significant neuroendocrine changes in a woman's life — the transition to menopause. In this review, we summarize recent studies of the neural and cognitive changes that unfold in the middle decade of life (ages 45-60), as a function of sex, reproductive stage, and sex steroid hormones. As the 'cognitive neuroscience of aging' field evolves, applying a women's health lens to the study of the aging brain will enhance the translation of these findings for both sexes and ensure that men and women get the full benefit of our research efforts. By ignoring the midlife window, we risk missing critical clues that could reveal sex-dependent risk factors of future neurodegenerative disease.

Addresses
[1] Department of Psychological and Brain Sciences, University of California, Santa Barbara, United States
[2] Neuroscience Research Institute, University of California, Santa Barbara, United States
[3] Departments of Psychiatry and Medicine, Harvard Medical School, United States
[4] Departments of Psychiatry and Obstetrics and Gynecology, Massachusetts General Hospital, United States
[5] Athinoula A. Martinos Brain Imaging Center, Massachusetts General Hospital, United States

Corresponding author: Jacobs, Emily G (emily.jacobs@psych.ucsb.edu)

Current Opinion in Behavioral Sciences 2018, **23**:84–91

This review comes from a themed issue on **Sex and gender**

Edited by **Carrie Ferrario, Jill Becker** and **Natalie Tronson**

https://doi.org/10.1016/j.cobeha.2018.03.009

Introduction

Over the last quarter century, a staggering number of brain imaging studies have probed the neural basis of age-related cognitive decline. Using multimodal brain imaging tools, we now have a clearer understanding of the morphological, neurochemical, and neurophysiological changes that accompany age-related declines in working memory, selective attention, inhibitory control, episodic memory and more (for review, see [1••]). These studies generally target adults over the age of 65, a historical precedent rooted in the average retirement age of U.S. wage-earners. An unintended consequence of this adopted standard is that it overlooks one of the most significant neuroendocrine changes in a woman's life — the transition to menopause. In turn, it obscures our understanding of sex-dependent pathways that may shape the brain early in the aging process.

The median age of menopause is 52.4 years [2]. The time between the first clinical appearance of decreased ovarian function (i.e. shorter inter-menstrual time periods) to menstrual irregularity and final amenorrhea is variable and protracted, occurring over several years [3]. The menopausal transition is marked by a decline in ovarian hormone production and is a time when many women report changes in memory and attention (e.g. 'menopause fog'). Two decades of rodent and nonhuman primate studies have established the role of sex hormones in the synaptic organization of the hippocampus and prefrontal cortex (PFC), and their impact on memory function [4••,5]. A parallel literature has emerged within the human cognitive neuroscience field to identify the role of sex hormones in memory circuitry in the human brain. In this review, we summarize recent studies of the neural and cognitive changes that unfold in the middle decade of life (ages 45–60), as a function of sex, reproductive stage, and sex steroid hormones. As the 'cognitive neuroscience of aging' field evolves, applying a sex dependent lens to the study of the aging brain will enhance the translation of these findings for both sexes and ensure that men and women get the full benefit of our research efforts. By ignoring the midlife window, we risk missing critical clues that could reveal sex-dependent risk factors of future neurodegenerative disease.

Sex hormone action in memory circuity — rodent and nonhuman primate studies

Nearly 50% of pyramidal neurons in the prefrontal cortex express estrogen receptors (ER), which hints at the powerful role estradiol plays in higher-order cognitive

functions [4••,5–7]. Estradiol, the main form of estrogen in mammals, acts on a broad set of cortical and subcortical brain regions to alter synaptic plasticity, regulate the synthesis and release of major neuromodulators, and influence memory performance [4••,5,8–10,11••,12]. Progesterone's role in higher-order cognitive functions is understudied, but for a recent review of progesterone's action in the central nervous system see [13,14].

In rodents and nonhuman primates, estradiol and progesterone signaling are critical components of cell survival and plasticity, and their effects can be measured across multiple spatial and temporal scales. At the epigenetic level, estradiol shapes hippocampal-dependent memory by inducing chromatin modifications that promote hippocampal plasticity [15]. At the synaptic level, estradiol regulates dendritic spine proliferation in the hippocampus and PFC [5]. In female macaques, surgical menopause leads to a 30% loss in spine density in hippocampal CA1 neurons, which is reversed by estradiol replacement [16]. Natural menopause reduces the density of perforated synapse spines in CA1 neurons, which is correlated with poorer recognition memory [17]. At the behavioral level, performance on PFC-dependent memory tasks is enhanced by cyclic estradiol administration in aged female macaques [11••,18•].

Animal studies are able to decouple the effects of reproductive aging from chronological aging via surgical menopause (ovariectomization) paradigms. These studies demonstrate that ovarian hormone depletion impacts hippocampal and PFC morphology and function, independent of the well-established influence of chronological aging. This body of work has made significant progress toward characterizing the synaptic basis of menopause-related memory decline [11••,19].

Sex differences and sex hormones shape memory function in midlife adults

Epidemiological surveys indicate that many women report increased forgetfulness and 'brain fog' during the menopausal transition [20]. Sex differences in memory performance, particularly verbal material, emerge post-puberty and are retained into adulthood. Although women's performance attenuates with menopause, a small female advantage is maintained in the healthy aging brain through midlife and old age. Despite these findings, less is known about memory changes in women during the menopausal transition compared with age-matched men, or sex differences in specific memory domains early in the aging process.

Rentz *et al.* [21] identified changes in memory function that occur in early midlife ($N = 212$, ages 45–55) as a function of sex, reproductive stage, and sex steroid hormone concentrations. To identify memory domains related to the perceived memory complaints in midlife women, the authors selected tests that are sensitive to executive and temporo-limbic dysfunction in clinically normal adults, including the 12-item Face-Name Associative Memory Exam and the 6-trial Selective Reminding Test (SRT). Women outperformed age-matched men across all memory measures. This held true until postmenopause, when the female advantage was attenuated. Among women, higher estradiol levels were associated with better memory performance.

In earlier work, the prospective Penn Ovarian Aging Study reported that reproductive senescence was associated with a decline in verbal fluency for midlife women [22]. In a systematic review of observational studies on cognitive performance in midlife women, Weber *et al.* [23] found that premenopausal and perimenopausal women outperformed postmenopausal women on measures of delayed verbal memory. In a large population study of sex differences in cognitive aging (Baltimore Longitudinal Study of Aging; $N = 1065–2127$; mean baseline age, ~65), older women continued to outperform men on verbal learning and memory, and showed a slower rate of cognitive decline in visual memory [24].

Sex differences and sex hormones shape memory circuitry in midlife — neuroimaging studies

Mounting evidence from human neuroimaging studies implicates sex steroids in the regulation of memory circuitry ([25–33]). This research builds on the pioneering work of Berman *et al.* [34] and Shaywitz *et al.* [35], who used pharmacological blockade and hormone replacement techniques to illustrate estradiol and progesterone's impact on regional brain activity in memory circuitry. These studies provide evidence that functional changes in estrogen receptor-rich regions of memory circuitry are tied to ovarian status. Thus, the depletion of ovarian hormones during menopause may impact specific neural circuits early in the aging process ([22,36••]).

In contrast, the largest randomized clinical trial of hormone replacement therapy (HT) in postmenopausal women found no benefit of HT for slowing the rate of cognitive decline and found an increased risk of dementia [37], although more recent work in midlife women challenges this finding (see [38–41]). Reconciling longstanding discrepancies between basic animal studies and large-scale clinical trials on estradiol's neural and cognitive effects is essential for advancing women's health [5,36,42–44]. A human cognitive neuroscience approach bridges preclinical and clinical perspectives by interrogating the role of sex steroid hormones in specific neural circuits. Ultimately, investigating the hormonal regulation of memory circuitry in the human brain could offer critical clues about why there is a higher frequency of women with memory disorders later in life [45].

Below we review recent findings on structural and functional changes in memory circuitry that unfold in the middle-aged brain.

Alterations in memory circuitry are evident by midlife

Age-related changes in neural activity during memory encoding and retrieval paradigms are well-established, with healthy older adults (aged 65+) showing altered responses in PFC and hippocampus relative to young adults (e.g. [46,47]). Now more attention is being paid to the neural and cognitive changes that unfold in the preceding decade, as adults enter midlife [48•,49]. Changes in memory encoding and retrieval performance and related neural activity are evident before 65 [48,50,51]. However, among the limited number of fMRI studies of memory function in midlife, none report changes in middle temporal lobe regions (when performance is matched across groups) and changes in PFC function are inconsistent [48,50]. Some studies report under-recruitment of prefrontal regions during source encoding in middle-aged relative to younger adults [51], and others report heightened PFC activation during spatial and temporal context memory retrieval in middle-aged adults [50]. These inconsistencies may be due to differences in the memory domain being investigated, differences in the ages being compared, lack of attention to activity in other regions within memory circuitry, and lack of attention to sex differences in study design and analysis.

While these studies represent an important step toward characterizing early changes in memory circuitry, few have examined the impact of sex or women's reproductive stage. This is surprising given that this time period captures the menopausal transition in women, and thus offers a unique opportunity to study the impact of gonadal hormones on memory function. In fact, one of the most consistently observed cognitive changes in women transitioning through menopause is in the domain of verbal learning and memory [21,22,52].

Impact of reproductive stage and sex steroids on memory circuitry

Episodic memory. Our group recently identified functional differences in memory circuitry in midlife, based on sex and women's reproductive stage [31]. In a population-based fMRI study, men and women (N = 200; age range, 45–55) performed a verbal memory encoding task during fMRI scanning. Task-evoked hippocampal responses differed by reproductive stage, despite minimal difference in chronological age. Across women, lower estradiol concentrations were related to more pronounced alterations in hippocampal connectivity and poorer performance on a subsequent memory retrieval task, strongly implicating sex steroids in the regulation of this circuitry. While the influence of menopausal status was greatest in the hippocampus, a number of sex differences were observed in prefrontal and parietal regions during verbal encoding in our midlife cohort. Men showed greater superior parietal activity and greater functional connectivity between PFC and posterior parietal cortex during encoding relative to women, irrespective of menopausal stage [31] (Figure 1).

Working memory. Menopausal status also shapes working memory-related PFC and hippocampal responses [30,31]. In a study of midlife adults (N = 142, age range 45–55), postmenopausal women recruited dorsolateral PFC more strongly than premenopausal women and showed less deactivation of the hippocampus during a verbal working memory task. This may represent a compensatory response since the magnitude of activity in these regions and the strength of functional connectivity between them were associated with working memory performance.

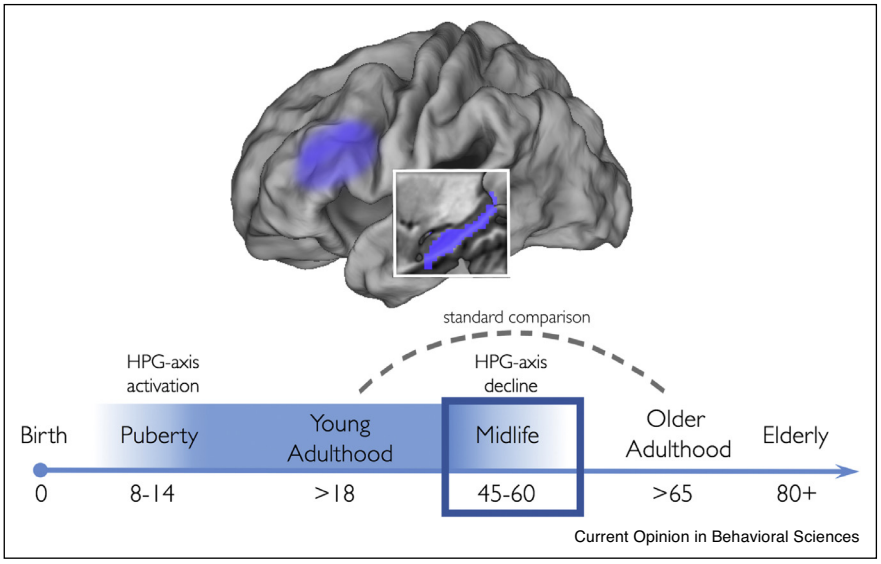
One of the most consistent patterns of age-related changes in brain activity is increased bilateral recruitment of frontal activity [53,54]. In our midlife sample, we observed a sex difference in whether this bilateral PFC response was related to WM performance. For women, brain–behavior relationships were left-lateralized. However, in men WM performance was related to bilateral responses in dorsolateral PFC and inferior parietal cortex. Notably, when subjects were analyzed as a single group, the bilateral brain–behavior relationship remained significant, obscuring the underlying sex-dependent nature of the finding. This raises the possibility that existing cognitive models describing the loss of hemispheric asymmetry with age (e.g. Hemispheric Asymmetry Reduction in Older Adults (HAROLD)) contain unexplained sex differences [55]. Alternatively, these models may reliably represent the data observed in men and women age 65+, while leaving open the possibility that sex differences are evident earlier in the aging process. For example, the timing of when age-related bihemispheric effects emerge may differ between men and women and only be revealed in studies targeting the early midlife window.

These findings underscore the importance of considering reproductive stage, not simply chronological age, to identify neural and cognitive changes that unfold in the middle decade of life. In keeping with preclinical evidence, these human findings suggest that the decline in ovarian estradiol production during menopause plays a role in shaping memory circuitry.

Sex differences in memory circuity

Memory circuitry is sexually dimorphic, with volumetric differences observed in the hippocampus, PFC, anterior cingulate cortex and inferior parietal cortex [56–59]. Sex differences in hippocampal volume emerge post-puberty, with larger bilateral hippocampi (adjusted for age and total intracranial volume) in females, even after menopause ([60–62], but see [56,63]). This effect may be regionally specific, with one of the most prominent sex

Figure 1



Top: Functional MRI studies reveal that some of the most robust task-evoked changes in the brain during the menopausal transition occur within PFC and hippocampus (white box depicts a medial hippocampal slice projected on a rendered brain; adapted from Refs. [30,31]. Bottom: Cognitive aging studies typically compare older adults >65 to young adults, overlooking the midlife period. Much like the groundswell of interest in the adolescent brain and the maturational changes that occur as gonadal hormones come 'on line', cognitive neuroscience is expanding its focus to the middle-aged brain, a transitional period when hormone production declines and age-related cognitive changes emerge. *Abbreviation*: HPG, hypothalamic–pituitary–gonadal axis.

differences in the hippocampal CA1 subfield [61]. An outstanding question is the extent to which the midlife decline in endogenous estradiol production alters hippocampal morphology in women. Recent findings from our group [62] suggest the presence of a subtle, ongoing process of reorganization of memory circuity during the menopausal transition. While gross hippocampal volume did not differ between pre-menopausal, peri-menopausal, and postmenopausal women in our study ($N = 193$), the structural covariance among regions in memory circuitry (hippocampus, dorsolateral PFC, ACC, and inferior parietal cortex) differed by menopausal status and was associated with group differences in memory performance.

Impact of estrogen supplementation on hippocampal morphology/function

A handful of recent studies have examined the effect of hormone replacement therapy (HT) in postmenopausal women on brain morphology. Albert *et al.* [32] investigated the impact of short-term estradiol supplementation on hippocampal volume in postmenopausal women ($N = 75$, age range 51–75). Women were postmenopausal and hormone-naïve at the start of the trial, and randomized to receive placebo, estradiol (1 mg), or estradiol (2 mg) continuously for three months. Structural MRI's were acquired at baseline and at the conclusion of the three-month trial. After three months of estradiol administration, bilateral posterior hippocampal volume was increased relative to baseline for women who received 2 mg estradiol. No difference was apparent in women receiving 1 mg or placebo.

The macrostructural changes evident in the hippocampus in response to estradiol supplementation may produce cognitive benefits (for a review, see [38]). Maki *et al.* [64] studied postmenopausal women (mean age 60 years) who began HT in perimenopause and continued their use in an uninterrupted pattern, relative to age-matched and education-matched hormone-naïve controls. Women who began HT in perimenopause had enhanced hippocampal activity during a verbal recognition task and better verbal memory performance relative to nonusers. When initiated early in menopausal transition, hormone replacement also appears to enhance cognitive-control related dorsolateral PFC activity and improve task-switching performance in women [33].

These human neuroimaging findings are consistent with recent rodent and nonhuman primate studies demonstrating estradiol's modulation of hippocampal and PFC structural plasticity and estradiol's protective effects against cognitive decline [5,11••,19]. For example, cyclic estradiol administration in postmenopausal female monkeys restores dorsolateral PFC spine density and the frequency of multisynaptic boutons to levels comparable to premenopausal females, and these synaptic-level changes are accompanied by enhanced working memory performance in estradiol-treated animals [11••]. Similarly, estradiol

supplementation reverses the decline in hippocampal spine density caused by surgical menopause [16].

Future studies

Knowledge about the normative changes that occur in the middle-aged brain is rapidly expanding, but outstanding questions remain. Below we highlight future research directions that would advance our understanding of how the brain changes in the earliest stages of the aging process.

Broaden cognitive domains of interest

Cognitive neuroscience studies of midlife and the menopausal transition focus primarily on the memory domain [21,26–28,30–32,51]. Future investigations would benefit from studying additional cognitive domains that may be sensitive to early age-related decline. For example, spatial navigation has emerged as a promising functional marker for detecting individuals at risk for dementia. While the effects of chronological aging on the brain's navigation system is well established [65,66], very little is known about how this system changes in midlife. Despite the widespread literature on sex differences in spatial cognition [67], there is scant research on sex differences in spatial abilities in the aging brain and the role sex steroid hormones play in this process. The effects of testosterone on spatial ability and spatial cognition in elderly men have been investigated [68], but there is a lack of normative data for women during the menopausal transition and for men in the middle decades of life.

Multimodal imaging — linking structure, function, and behavior

Studies that combine multi-modal neuroimaging, endocrinology, and behavioral assessments are necessary to understand how the midlife brain changes at the neurochemical, neurophysiological and neuroanatomical levels. How do hormone-dependent macrostructural changes in grey and white matter impact intrinsic brain networks, task-evoked functional BOLD responses, and cognitive performance? Recent analyses carried out with respect to the aging brain could serve as a guide ([69,70]). Identifying midlife alterations within large-scale structural and functional brain networks could give us clues about an individual's future risk for cognitive decline [71,72]. Further, longitudinal studies using high-resolution imaging of hippocampal subfields and other cortical and subcortical regions would improve our understanding of the normative morphological changes that occur in midlife as ovarian hormone production declines.

Hormonal regulation of neuromodulatory systems

Using molecular PET imaging, multinuclear magnetic resonance spectroscopy, pharmacological fMRI, and imaging genetics approaches, neuroimaging studies have begun to investigate sex hormones' influence on the activity of major neuromodulatory systems [73–77]. More work in this arena will be key for deepening our understanding of the pathways through which sex hormones shape higher-order cognitive function. For example, longstanding experimental evidence in animals [8,9,78,79] and indirect evidence in humans [25] suggests that estradiol impacts PFC function and working memory in part by modulating activity within the dopaminergic system. Applying these approaches to the aging brain would help clarify the relationship between the midlife decline in neuroactive gonadal hormones, dopaminergic signaling, and working memory dysfunction. Although dopamine receptor distribution and dopamine synthesis capacity change with age [80] it is unclear whether biological sex or sex hormones alter these relationships.

Molecular PET imaging techniques can be used to characterize the influence of biological sex and sex hormone concentrations on properties of neurotransmitter systems. For example, by pairing PET imaging with pharmacological manipulation of the dopamine system researchers can indirectly assess dopamine release (with radioligand [11C]raclopride) and synthesis capacity ([18F]Fluorometatyrosine). This method could provide insights into sex differences in basal dopamine receptor occupancy, stimulated dopamine release, and dopamine synthesis capacity. This kind of study, which is currently underway (Jacobs and D'Esposito, 2018), would expand our fundamental knowledge of how biological sex and sex steroid hormones shape dopamine neurotransmission in the human brain.

Further, taking into account genetic variability in neuromodulatory and neurotrophic pathways could reveal individual differences in the impact of reproductive aging on cognitive function. For example, early evidence suggests that subpopulations of women may be more resilient to the midlife decline in sex hormones based on genetic variability in neurotransmitter (COMT val158met) or neurotrophic (BDNF val66met) pathways [74,81–83].

Conclusion

The proportion of older adults in the US population is growing rapidly (United States Census, 2010) and three out of four report problems with their memory [84]. Maintaining intact memory function with age may be one of the greatest public health challenges of our time. Intervening early with high risk individuals is critical for the attenuation and prevention of disability, but early targets for treatment have not been identified. Given evidence that women have a higher frequency of memory disorders than men later in life [45], applying a sex-dependent lens to the study of the aging brain will help identify early antecedents of future memory decline. In rodents and nonhuman primates, sex hormones shape the synaptic organization of the hippocampus and PFC and influence memory function [4••,5]. Now, an emerging body of research has begun to identify sex hormones' role

in memory circuitry regions in the human brain. In women, the loss of ovarian estradiol during menopause impacts PFC and hippocampal function at the level of structural morphology, task-evoked fMRI BOLD, and performance on demanding memory tasks. Moving forward, using convergent techniques from systems and cognitive neuroscience and fostering collaborations between basic and clinical scientists will be critical for understanding the normative changes that unfold in the middle-aged healthy brain and for identifying sex-dependent therapeutic targets that can be applied prior to overt cognitive decline.

Conflict of interest statement

NeuroPhase (JMG).

Acknowledgements

This work was supported by the Office for Research on Women's Health — National Institute on Child Health and Development K12 HD051959 (EGJ), the National Institute of Mental Health R01 MH090291 (JMG), and a Brain and Behavior Research Foundation NARSAD Young Investigator Grant 26344 (EGJ).

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. •• Cabeza R, Nyberg L, Park DC (Eds): *Cognitive Neuroscience of Aging: Linking Cognitive and Cerebral Aging*. Oxford University Press; 2016.

Comprehensive set of review articles summarizing our current understanding of the neural basis of age-related cognitive decline. Park and Festini's chapter on the middle-aged brain synthesizes our limited, but growing, understanding of early age-related neural and cognitive changes.

2. Gold EB, Bromberger J, Crawford S, Samuels S, Greendale GA, Harlow SD, Skurnick J: **Factors associated with age at natural menopause in a multiethnic sample of midlife women**. *Am J Epidemiol* 2001, **153**:865-874.

3. Harlow SD, Gass M, Hall JE, Lobo R, Maki P, Rebar RW, Sherman S, Sluss PM, de Villiers TJ: **Executive summary of the stages of reproductive aging workshop+ 10: addressing the unfinished agenda of staging reproductive aging**. *Climacteric* 2012, **15**:105-114.

4. •• Frick KM, Tuscher JJ, Koss WA, Kim J, Taxier LR: **Estrogenic regulation of memory consolidation: a look beyond the hippocampus, ovaries, and females**. *Physiol Behav* 2018, **187**:57-66.

Comprehensive review of sex differences in the molecular mechanisms underlying estrogen-induced memory consolidation.

5. Hara Y, Waters EM, McEwen BS, Morrison JH: **Estrogen effects on cognitive and synaptic health over the lifecourse**. *Physiol Rev* 2015, **95**:785-807.

6. Wang AC, Hara Y, Janssen WG, Rapp PR, Morrison JH: **Synaptic estrogen receptor-a levels in prefrontal cortex in female rhesus monkeys and their correlation with cognitive performance**. *J Neurosci* 2010, **30**:12770-12776.

7. Bean LA, Ianov L, Foster TC: **Estrogen receptors, the hippocampus, and memory**. *Neuroscientist* 2014, **20**:534-545.

8. Chisholm NC, Packard AR, Koss WA, Juraska JM: **The effects of long-term treatment with estradiol and medroxyprogesterone acetate on tyrosine hydroxylase fibers and neuron number in the medial prefrontal cortex of aged female rats**. *Endocrinology* 2012, **153**:4874-4882.

9. Almey A, Milner TA, Brake WG: **Estrogen receptors in the central nervous system and their implication for dopamine-dependent cognition in females**. *Hormones Behav* 2015, **74**: 125-138.

10. Galvin C, Ninan I: **Regulation of the mouse medial prefrontal cortical synapses by endogenous estradiol**. *Neuropsychopharmacology* 2014, **39**:2086-2094.

11. •• Hara Y, Yuk F, Puri R, Janssen WG, Rapp PR, Morrison JH: **Estrogen restores multisynaptic boutons in the dorsolateral prefrontal cortex while promoting working memory in aged rhesus monkeys**. *J Neurosci* 2016, **36**:901-910.

This paper adds a new layer to an extensive body of work from the Morrison lab demonstrating estrogen's role in synaptic plasticity and dendritic remodeling in PFC, and working memory performance in aged female monkeys.

12. Rossetti MF, Cambiasso MJ, Holschbach MA, Cabrera R: **Oestrogens and progestagens: synthesis and action in the brain**. *J Neuroendocrinol* 2016, **28**.

13. Schumacher M, Mattern C, Ghoumari A, Oudinet JP, Liere P, Labombarda F, Sitruk-Ware R, De Nicola AF, Guennoun R: **Revisiting the roles of progesterone and allopregnanolone in the nervous system: resurgence of the progesterone receptors**. *Prog Neurobiol* 2014, **113**:6-39.

14. Barros LA, Tufik S, Andersen ML: **The role of progesterone in memory: an overview of three decades**. *Neurosci Biobehav Rev* 2015, **49**:193-204.

15. Fortress AM, Frick KM: **Epigenetic regulation of estrogen-dependent memory**. *Frontiers Neuroendocrinol* 2014, **35**: 530-549.

16. Dumitriu D, Rapp PR, McEwen BS, Morrison JH: **Estrogen and the aging brain: an elixir for the weary cortical network**. *Ann N Y Acad Sci* 2010, **1204**:104-112.

17. Hara Y, Park CS, Janssen WG, Roberts MT, Morrison JH, Rapp PR: **Synaptic correlates of memory and menopause in the hippocampal dentate gyrus in rhesus monkeys**. *Neurobiol Aging* 2012, **33**:421 e17–28.

18. • Kohama SG, Renner L, Landauer N, Weiss AR, Urbanski HF, Park B, Voytko ML, Neuringer M: **Effect of ovarian hormone therapy on cognition in the aged female rhesus macaque**. *J Neurosci* 2016, **36**:10416-10424.

The authors examined the impact of early, continuous hormone replacement on cognition in female monkeys following surgical menopause. Estradiol supplementation had long-term cognitive benefits on tests of memory and attention. Estradiol-treated animals out-performed untreated ovariectomized animals and untreated ovarian intact animals. Preclinical studies like this are important for clarifying how formulation and age of initiation of hormonal regimens shape cognitive outcomes.

19. Morrison JH, Baxter MG: **The ageing cortical synapse: hallmarks and implications for cognitive decline**. *Nat Rev Neurosci* 2012, **13**:240-250.

20. Greendale GA, Derby CA, Maki PM: **Perimenopause and cognition**. *Obstet Gynecol Clin North Am* 2011, **38**:519-535.

21. Rentz DM, Weiss BK, Jacobs EG, Cherkerzian S, Klibanski A, Remington A, Aizley H, Goldstein JM: **Sex differences in episodic memory in early midlife: impact of reproductive aging**. *Menopause* 2017, **24**:400-408.

22. Epperson CN, Sammel MD, Freeman EW: **Menopause effects on verbal memory: findings from a longitudinal community cohort**. *J Clin Endocrinol Metab* 2013, **98**:3829-3838.

23. Weber MT, Maki PM, McDermott MP: **Cognition and mood in perimenopause: a systematic review and meta-analysis**. *J Steroid Biochem Mol Biol* 2014, **142**:90-98.

24. McCarrey AC, An Y, Kitner-Triolo MH, Ferrucci L, Resnick SM: **Sex differences in cognitive trajectories in clinically normal older adults**. *Psychol Aging* 2016, **31**:166-175.

25. Jacobs E, D'Esposito M: **Estrogen shapes dopamine-dependent cognitive processes: implications for women's health**. *J Neurosci* 2011, **31**:5286-5293.

26. Epperson CN, Amin Z, Ruparel K, Gur R, Loughead J: **Interactive effects of estrogen and serotonin on brain activation during working memory and affective processing in menopausal women**. *Psychoneuroendocrinology* 2012, **37**:372-382.

27. Hampson E, Morley EE: **Estradiol concentrations and working memory performance in women of reproductive age**. *Psychoneuroendocrinology* 2013, **38**:2897-2904.

28. Shanmugan S, Epperson CN: **Estrogen and the prefrontal cortex: towards a new understanding of estrogen's effects on executive functions in the menopause transition**. *Hum Brain Mapp* 2014, **35**:847-865.

29. Jacobs EG, Holsen LM, Lancaster K, Makris N, Whitfield-Gabrieli S, Remington A, Weiss B, Buka S, Klibanski A, Goldstein JM: **17β-Estradiol differentially regulates stress circuitry activity in healthy and depressed women**. *Neuropsychopharmacology* 2015, **40**:566-576.

30. Jacobs EG, Weiss B, Makris N, Whitfield-Gabrieli S, Buka SL, Klibanski A, Goldstein JM: **Reorganization of functional networks in verbal working memory circuitry in early midlife: the impact of sex and menopausal status**. *Cereb Cortex* 2017, **27**:2857-2870.

31. Jacobs EG, Weiss BK, Makris N, Whitfield-Gabrieli S, Buka SL, Klibanski A, Goldstein JM: **Impact of sex and menopausal status on episodic memory circuitry in early midlife**. *J Neurosci* 2016, **36**:10163-10173.

32. Albert K, Hiscox J, Boyd B, Dumas J, Taylor W, Newhouse P: **Estrogen enhances hippocampal gray-matter volume in young and older postmenopausal women: a prospective dose–response study**. *Neurobiol Aging* 2017, **56**:1-6.

33. Girard R, Météreau E, Thomas J, Pugeat M, Qu C, Dreher JC: **Hormone therapy at early post-menopause increases cognitive control-related prefrontal activity**. *Sci Rep* 2017:7.

34. Berman KF, Schmidt PJ, Rubinow DR, Danaceau MA, Van Horn JD, Esposito G, Ostrem JL, Weinberger DR: **Modulation of cognition-specific cortical activity by gonadal steroids: a positron-emission tomography study in women**. *Proc Natl Acad Sci U S A* 1997, **94**:8836-8841.

35. Shaywitz SE, Shaywitz BA, Pugh KR, Fulbright RK, Skudlarski P, Mencl WE, Constable RT, Naftolin F, Palter SF, Marchione KE *et al.*: **Effect of estrogen on brain activation patterns in postmenopausal women during working memory tasks**. *JAMA* 1999, **281**:1197-1202.

36. •• Brinton RD, Yao J, Yin F, Mack WJ, Cadenas E: **Perimenopause as a neurological transition state**. *Nat Rev Endocrinol* 2015, **11**:393-405.

An essential review of the neurological changes that accompany perimenopause, with an emphasis on cellular and molecular events. Unique perspective on estrogen's regulation of the brain's bioenergetic capabilities.

37. Shumaker SA, Legault C, Rapp SR, Thal L, Wallace RB, Ockene JK, Hendrix SL, Jones BN III, Assaf AR, Jackson RD *et al.*: **Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial**. *JAMA* 2003, **289**:2651-2662.

38. Daniel JM, Witty CF, Rodgers SP: **Long-term consequences of estrogens administered in midlife on female cognitive aging**. *Hormones Behav* 2015, **74**:77-85.

39. McCarrey AC, Resnick SM: **Postmenopausal hormone therapy and cognition**. *Hormones Behav* 2015, **74**:167-172.

40. Henderson VW, John JAS, Hodis HN, McCleary CA, Stanczyk FZ, Shoupe D, Kono N, Dustin L, Allayee H, Mack WJ: **Cognitive effects of estradiol after menopause. A randomized trial of the timing hypothesis**. *Neurology* 2016, **87**:699-708.

41. Prakapenka AV, Hiroi R, Quihuis AM, Carson C, Patel S, Berns-Leone C, Fox C, Sirianni RW, Bimonte-Nelson HA: **Contrasting effects of individual versus combined estrogen and progestogen regimens as working memory load increases in middle-aged ovariectomized rats: one plus one does not equal two**. *Neurobiol Aging* 2017.

42. Morrison JH, Briton RD, Schmidt PJ, Gore AC: **Estrogen, menopause, and the aging brain: how basic neuroscience can inform hormone therapy in women**. *J Neurosci* 2006, **26**:10332-10348.

43. Maki PM, Henderson VW: **Hormone therapy, dementia, and cognition: the Women's Health Initiative 10 years on**. *Climacteric* 2012, **15**:256-262.

44. Boulware MI, Kent BA, Frick KM: **The impact of age-related ovarian hormone loss on cognitive and neural function**. *Curr Top Behav Neurosci* 2012, **10**:165-184.

45. Mielke MM, Vemuri P, Rocca WA: **Clinical epidemiology of Alzheimer's disease: assessing sex and gender differences**. *Clin Epidemiol* 2014, **6**:37-48.

46. Rajah MN, Maillet D, Grady CL: **Episodic memory in healthy older adults: the role of prefrontal and parietal cortices**. In *The Wiley Handbook on the Cognitive Neuroscience of Memory.* Edited by Addis DR, Barense, Duarte A. John Wiley & Sons, Ltd.; 2015:347-370.

47. Pudas S, Josefsson M, Rieckmann A, Nyberg L: **Longitudinal evidence for increased functional response in frontal cortex for older adults with hippocampal atrophy and memory decline**. *Cereb Cortex* 2017:1-13.

48. • Park H, Kennedy KM, Rodrigue KM, Hebrank A, Park DC: **An fMRI study of episodic encoding across the lifespan: changes in subsequent memory effects are evident by middle-age**. *Neuropsychologia* 2013, **51**:448-456.

One of the first fMRI studies to demonstrate early age-related alterations in neural activity during a memory encoding/retrieval task in middle-aged adults.

49. Park D, Festini S: **The middle aged brain: a cognitive neuroscience perspective**. In *The Cognitive Neuroscience of Aging: Linking Cognitive and Cerebral Aging.* Edited by Cabeza br, Park. Oxford University Press; 2016:363-388.

50. Kwon D, Maillet D, Pasvanis S, Ankudowich E, Grady CL, Rajah MN: **Context memory decline in middle aged adults is related to changes in prefrontal cortex function**. *Cereb Cortex* 2016, **26**:2440-2460.

51. Cansino S, Estrada-Manilla C, Trejo-Morales P, Pasaye-Alcaraz EH, Aguilar-Castaneda E, Salgado-Lujambio P, Sosa-Ortiz AL: **fMRI subsequent source memory effects in young, middle-aged and old adults**. *Behav Brain Res* 2015, **280**:24-35.

52. Berent-Spillson A, Persad CC, Love T, Sowers M, Randolph JF, Zubieta JK, Smith YR: **Hormonal environment affects cognition independent of age during the menopause transition**. *J Clin Endocrinol Metab* 2012, **97**:E1686-E1694.

53. Reuter-Lorenz PA, Cappell KA: **Neurocognitive aging and the compensation hypothesis**. *Curr Dir Psychol Sci* 2008, **17**:177-182.

54. Reuter-Lorenz PA, Jonides J, Smith EE, Hartley A, Miller A, Marshuetz C, Koeppe RA: **Age differences in the frontal lateralization of verbal and spatial working memory revealed by PET**. *J Cogn Neurosci* 2000, **12**:174-187.

55. Cabeza R: **Hemispheric asymmetry reduction in older adults: the HAROLD model**. *Psychol Aging* 2002, **17**:85-100.

56. Ruigrok AN, Salimi-Khorshidi G, Lai MC, Baron-Cohen S, Lombardo MV, Tait RJ, Suckling J: **A meta-analysis of sex differences in human brain structure**. *Neurosci Biobehav Rev* 2014, **39**:34-50.

57. Giedd JN, Raznahan A, Mills KL, Lenroot RK: **Review: magnetic resonance imaging of male/female differences in human adolescent brain anatomy**. *Biol Sex Differ* 2012, **3**:19.

58. Goldstein JM, Seidman LJ, Horton NJ, Makris N, Kennedy DN, Caviness VS Jr, Faraone SV, Tsuang MT: **Normal sexual dimorphism of the adult human brain assessed by in vivo magnetic resonance imaging**. *Cereb Cortex* 2001, **11**:490-497.

59. Abbs B, Liang L, Makris N, Tsuang M, Seidman LJ, Goldstein JM: **Covariance modeling of MRI brain volumes in memory circuitry in schizophrenia: sex differences are critical**. *NeuroImage* 2011, **56**:1865-1874.

60. Satterthwaite TD, Vandekar S, Wolf DH, Ruparel K, Roalf DR, Jackson C, Elliot MA, Davatzikos C: **Sex differences in the effect of puberty on hippocampal morphology**. *J Am Acad Child Adol Psychiatry* 2014, **53**:341-350.

61. Gur RE, Gur RC: **Sex differences in brain and behavior in adolescence: findings from the Philadelphia neurodevelopmental cohort**. *Neurosci Biobehav Rev* 2016, **70**:159-170.

62. Seitz J, Kubicki M, Jacobs EG, Cherkerzian S, Weiss BK, Papadimitriou G, Palig Mouradian P, Buka S, Jill M, Goldstein JM, Makris N: *Impact of sex and reproductive status on memory circuitry structure and function in early midlife using structural covariance analysis* 2018. under review.

63. Goddings AL, Mills KL, Clasen LS, Giedd JN, Viner RM, Blakemore SJ: **The influence of puberty on subcortical brain development**. *Neuroimage* 2014, **88**:242-251.

64. Maki PM, Dennerstein L, Clark M, Guthrie J, LaMontagne P, Fornelli D, Little D, Henderson VW, Resnick SM: **Perimenopausal use of hormone therapy is associated with enhanced memory and hippocampal function later in life**. *Brain Res* 2011, **1379**:232-243.

65. Lester AW, Moffat SD, Wiener JM, Barnes CA, Wolbers T: **The aging navigational system**. *Neuron* 2017, **95**:1019-1035.

66. Bohbot VD, McKenzie S, Konishi K, Fouquet C, Kurdi V, Schachar R, Boivin M, Robaey P: **Virtual navigation strategies from childhood to senescence: evidence for changes across the life span**. *Frontiers Aging Neurosci* 2012, **4**:1-10.

67. Moffat SD, Hampson E, Hatzipantelis M: **Navigation in a "virtual" maze: sex differences and correlation with psychometric measures of spatial ability in humans**. *Evolut Hum Behav* 1998, **19**:73-87.

68. Moffat SD: **Effects of testosterone on cognitive and brain aging in elderly men**. *Ann N Y Acad Sci* 2005, **1055**:80-92.

69. Reijmer YD, Schultz AP, Leemans A, O'sullivan MJ, Gurol ME, Sperling R, Greenberg SM, Viswanathan A, Hedden T: **Decoupling of structural and functional brain connectivity in older adults with white matter hyperintensities**. *Neuroimage* 2015, **117**:222-229.

70. Fell AM, Walhovd KB: **Multimodal imaging of the aging brain**. In *The Cognitive Neuroscience of Aging: Linking Cognitive and Cerebral Aging*. Edited by Cabeza br, Park. Oxford University Press; 2016:131-153.

71. Siman-Tov T, Bosak N, Sprecher E, Paz R, Eran A, Aharon-Peretz J, Kahn I: **Early age-related functional connectivity decline in high-order cognitive networks**. *Frontiers Aging Neurosci* 2017, **8**:330.

72. Scheinost D, Finn ES, Tokoglu F, Shen X, Papademetris X, Hampson M, Constable RT: **Sex differences in normal age trajectories of functional brain networks**. *Hum Brain Mapp* 2015, **36**:1524-1535.

73. Shanmugan S, Loughead J, Nanga RPR, Elliott M, Hariharan H, Appleby D, Kim D, Ruparel K, Reddy R, Brown TE, Epperson CN: **Lisdexamfetamine effects on executive activation and neurochemistry in menopausal women with executive function difficulties**. *Neuropsychopharmacology* 2017, **42**:437-445.

74. Wei SM, Baller EB, Kohn PD, Kippenhan JS, Kolachana B, Soldin SJ, Rubinow DR, Schmidt PJ, Berman KF: **Brain-derived neurotrophic factor Val66Met genotype and ovarian steroids interactively modulate working memory-related hippocampal function in women: a multimodal neuroimaging study**. *Mol Psychiatry* 2018, **23**:1066-1075.

75. Barth C, Villringer A, Sacher J: **Sex hormones affect neurotransmitters and shape the adult female brain during hormonal transition periods**. *Frontiers Neurosci* 2015:9.

76. Sinclair D, Purves-Tyson TD, Allen KM, Weickert CS: **Impacts of stress and sex hormones on dopamine neurotransmission in the adolescent brain**. *Psychopharmacology* 2014, **231**:1581-1599.

77. Newhouse P, Dumas J: **Estrogen–cholinergic interactions: implications for cognitive aging**. *Hormones Behav* 2015, **74**:173-185.

78. Becker JB: **Oestrogen effects on dopaminergic function in striatum**. In *Neuronal and Cognitive Effects of Oestrogens*. Edited by Chadwick DJ, Goode JA. Wiley; 2000:134-145.

79. Sárvári M, Deli L, Kocsis P, Márk L, Maász G, Hrabovszky E, Gajári D, Tihanyi K: **Estradiol and isotype-selective estrogen receptor agonists modulate the mesocortical dopaminergic system in gonadectomized female rats**. *Brain Res* 2014, **1583**:1-11.

80. Berry AS, Shah VD, Baker SL, Vogel JW, O'Neil JP, Janabi M, Schimmer HD, Marks SM, Jagust WJ: **Aging affects dopaminergic neural mechanisms of cognitive flexibility**. *J Neurosci* 2016, **36**:12559-12569.

81. Kennedy KM, Reese ED, Horn MM, Sizemore AN, Unni AK, Meerbrey ME, Kalich AG, Rodrigue KM: **BDNF val66met polymorphism affects aging of multiple types of memory**. *Brain Res* 2015, **1612**:104-117.

82. Konishi K, Cherkerzian S, Jacobs EG, Weiss BK, Rentz DM *et al.*: **Impact of BDNF and sex on maintaining intact memory function in early midlife**. *Abstract, 56th Annual Meeting of the American College of Neuropsychopharmacology; Palm Springs, CA: 2017. (Manuscript under review) December 2017*.

83. Wei SM, Eisenberg DP, Kohn PD, Kippenhan JS, Kolachana BS, Weinberger DR, Berman KF: **Brain-derived neurotrophic factor Val66Met polymorphism affects resting regional cerebral blood flow and functional connectivity differentially in women versus men**. *J Neurosci* 2012, **32**:7074-7081.

84. Koivisto K, Reinikainen KJ, Hanninen T, Vanhanen M, Helkala EL *et al.*: **Prevalence of age-associated memory impairment in a randomly selected population from eastern Finland**. *Neurology* 1995, **45**:741-747.