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The Middle-Aged Brain: Biological sex and sex hormones shape memory circuitry

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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 Cabeza, Nyberg & Park, 2016). 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 (Gold et al., 2001). 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. 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 (Frick et al., 2017, Hara et al. 2015). 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

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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.

I. Sex hormone action in memory circuitry – 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 (Wang et al., 2010; Bean et al., 2014; Hara et al., 2015; Frick et al. 2017). 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 (Chisholm et al., 2012; Hara et al., 2015; Almey et al., 2015; Galvin and Ninan, 2014; Hara et al. 2016; Rossetti et al., 2016; Frick et al., 2017). 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 Schumacher et al., 2014 and Barros et al., 2015.

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 (Fortress and Frick, 2014). At the synaptic level, estradiol regulates dendritic spine proliferation in the hippocampus and PFC (Hara et al., 2015). In female macaques, surgical menopause leads to a 30% loss in spine density in hippocampal CA1 neurons, which is reversed by estradiol replacement (Dumitriu et al., 2010). Natural menopause reduces the density of perforated synapse spines in CA1 neurons, which is correlated with poorer recognition memory (Hara et al., 2012). At the behavioral level, performance on PFC-dependent memory tasks is enhanced by cyclic estradiol administration in aged female macaques (Kohama et al., 2016, Hara et al., 2016).

Animal studies are able to decouple the effects of reproductive aging from chronological aging via surgical menopause (ovariectomy) 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 towards characterizing the synaptic basis of menopause-related memory decline (Morrison et al. 2012; Hara et al., 2016).

II. 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 (Greendale et al. 2011). 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 and colleagues (2017) 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 (Epperson et al., 2013). In a systematic review of observational studies on cognitive performance in midlife women, Weber and colleagues (2014) 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 (McCarrey et al., 2016).

III. 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 (Jacobs and D’Esposito, 2011; Epperson et al., 2012; Hampson and Morley, 2013; Shanmugan and Epperson, 2014; Jacobs et al., 2015; Jacobs et al., 2016; Jacobs et al., 2017; Albert et al., 2017; Girard et al., 2017). This research builds on the pioneering work of Berman (1997) and Shaywitz (1999), 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 (Brinton et al., 2015; Epperson and Freeman, 2013).

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 (Shumaker et al., 2003), although more recent work in midlife women challenges this finding (see Daniel et al., 2015; McCarrey and Resnick, 2015; Henderson et al., 2016; and Prakapenka et al., 2017). Reconciling long-standing discrepancies between basic animal studies and large-scale clinical trials on estradiol's neural and cognitive effects is essential for advancing women's health (Morrison et al., 2006; Hara et al., 2015; Maki & Henderson, 2012; Boulware, Kent and Frick, 2012; Brinton et al., 2015). 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 (Mielke et al., 2014).

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. Rajah et al., 2015; Pudas et al., 2017). Now more attention is being paid to the neural and cognitive changes that unfold in the preceding decade, as adults enter midlife (Park et al., 2013; Park and Festini, 2016). Changes in memory encoding and retrieval performance and related neural activity are evident before 65 (Kwon et al., 2016; Cansino et al., 2015; Park et al., 2013). 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 (Kwon et al., 2016; Park et al., 2013). Some studies report under-recruitment of prefrontal regions during source encoding in middle-aged relative to younger adults (Cansino et al., 2015), and others report heightened PFC activation during spatial and temporal context memory retrieval in middle-aged adults (Kwon, et al. 2016). 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 (Epperson et al., 2013; Berent-Spillion et al., 2012; Rentz et al., 2017).

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 (Jacobs et al., 2017). 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 (Jacobs et al., 2017).

Working Memory—Menopausal status also shapes working memory-related PFC and hippocampal responses (Jacobs et al., 2016). 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 (Davis et al., 2008). 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 (Cabeza 2002). 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 circuitry

Memory circuitry is sexually dimorphic, with volumetric differences observed in the hippocampus, PFC, anterior cingulate cortex and inferior parietal cortex (Ruigrok et al, 2014; Giedd et al., 2012; Goldstein et al., 2001; Abbs, et al, 2011). Sex differences in hippocampal volume emerge post-puberty, with larger bilateral hippocampi (adjusted for age and total intracranial volume) in females, even after menopause (Satterthwaite et al., 2014, Gur et al., 2016, Seitz et al., *under review*, but see Ruigrok et al, 2014 and Goddings et al, 2014). This effect may be regionally specific, with one of the most prominent sex differences in the hippocampal CA1 subfield (Gur et al., 2016). 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 (Seitz et al., *under review*) suggests the presence of a subtle, ongoing process of reorganization of memory circuitry during the menopausal transition. While gross hippocampal volume did not differ between pre-, peri-, 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 and colleagues (2017) 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 2mg 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 Daniel et al., 2015). Maki and colleagues (2011) studied postmenopausal women (mean age 60 years) who began HT in perimenopause and continued their use in an uninterrupted pattern, relative to age- 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 (Girard et al., 2017).

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 (Morrison et al., 2012, Hara et al., 2015, Hara et al., 2016). 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 (Hara et al., 2016). Similarly, estradiol supplementation reverses the decline in hippocampal spine density caused by surgical menopause (Dumitriu et al., 2010).

IV. 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 (Epperson et al., 2012; Berent-Spillson et al., 2012, Hampson and Morley, 2013; Shanmugan and Epperson, 2014; Jacobs et al., 2016; Jacobs et al., 2017; Albert et al., 2017; Girard et al., 2017, Rentz et al., 2017). 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 (Lester et al., 2017, Bohbot et al., 2012), very little is known about how this system changes in midlife. Despite the widespread literature on sex differences in spatial cognition (Moffatt et al., 1998), 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 (Moffat, 2005), 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 (Reijmer et al., 2015; Fell et al, 2016). Identifying midlife alterations within large-scale structural and functional brain networks could give us clues about an individual's future risk for cognitive decline (Siman-Tav et al., 2017, Scheinost et al., 2015). 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 (Shanmugan et al., 2016; Wei et al., 2017; Barth et al., 2015; Sinclair et al., 2014, Newhouse and Dumas, 2015). 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 (Becker 2000, Chisholm et al., 2012, Sárvári et al., 2014, Almey et al., 2015) and indirect evidence in humans (Jacobs and D'Esposito, 2011) 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 (Berry et al., 2016) 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 (Wei et al., 2017, Kennedy et al., 2015; Konishi et al, 2018).

V. 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 (Koivisto et al., 1995). 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 (Mielke et al., 2014), 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 (Frick et al., 2017, Hara et al. 2015). 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.

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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 Jacobs et al., 2016, 2017). **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. *HPG*, Hypothalamic-Pituitary-Gonadal axis.