Ovarian hormones:

a long overlooked but critical contributor to cognitive brain structures and function

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Graphical abstract

This review summarizes historical trends that have led to a knowledge gap in the role of ovarian hormones in neuroscience, synthesizes recent findings on ovarian hormone contributions to cognitive brain structures and function, and highlights areas ripe for future work.

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Abstract

Cognitive neuroscience research has traditionally overlooked half of the population. Arguing that variability in ovarian hormones confounds empirical findings, girls and women have been excluded from research for decades. But times are changing. This review summarizes historical trends that have led to a knowledge gap in the role of ovarian hormones in neuroscience, synthesizes recent findings on ovarian hormone contributions to cognitive brain structures and function, and highlights areas ripe for future work. This is accomplished by reviewing research that has leveraged natural experiments in humans across the lifespan that focus on puberty, the menstrual cycle, hormonal contraceptive use, menopause, and menopausal hormone therapy. Although findings must be considered in light of study designs (e.g., sample characteristics and group comparisons versus randomized crossover trials), across natural experiments there is consistent evidence for associations of estradiol with cortical thickness, especially in frontal regions, and hippocampal volumes, as well as with frontal regions, during cognitive processing. There are also emerging investigations of resting state connectivity and progesterone along with exciting opportunities for future work, particularly concerning biopsychosocial moderators of and individual differences in effects in novel natural experiments. Thus, delineating complex ovarian hormone contributions to cognitive brain structures and function will advance neuroscience.

Introduction

From the molecular mechanisms subserving perception to the neural networks underlying verbal memory, cognitive neuroscience research has transformed understanding of the brain. Unfortunately, the extent to which research findings generalize to female animals and humans is unclear because they have been excluded from research for decades, with scientists arguing—despite sound evidence to the contrary—that hormone variations confound empirical work[1, 2]. Recent research, however, has begun to explicate the noteworthy role of human ovarian hormones in cognitive neuroscience, revealing that women are not intrinsically more variable than men and that sex hormones are not confounds, but rather, paramount to the neural anatomy and psychophysiology of all individuals.

Ovarian hormones in cognitive neuroscience: a timely investigation

There are several reasons for the paradigm shift. First, there is ever-mounting evidence for sex differences in the human brain coming from systematic reviews, meta-analyses, and journal special issues[3-6]. Differences span overall volume, regional morphology, trajectories of development, localized function, and patterns of connectivity. Second, there are indications that some neuroscientific findings in one sex do not generalize to the other. One example concerns the active ingredient in common sleep aids (zolpidem), which metabolizes differently in men and women, and, thus, impacts next-morning cognitive function differentially in the sexes. Because sex differences in biological responses to zolpidem were not initially investigated, women were given doses based on weight distributions in men and were at risk (e.g., for morning motor vehicle accidents) until dosage guidelines were modified[7]. Third, the 1993 National Institutes of Health Revitalization Act requires the inclusion of women and the examination of sex differences in clinical research; this was followed by a 2014 mandate to consider sex as a biological variable in basic

research[8, 9]. The study of ovarian hormone contributions to cognitive neuroscience naturally stems from sex differences research, as hormones are plausible antecedents and correlates of the differences.

Ovarian hormones and natural experiments

The primary hormones secreted by the ovaries are estradiol and progesterone; the former is a type of estrogen and the latter a type of progestagen. Both pass through the blood–brain barrier and have receptors throughout the brain[10]. Specifically, estradiol receptors (ERα and ERβ) are present throughout areas of the brain involved in cognitive functions, including the hippocampus and various cortical structures, especially the prefrontal cortex (PFC)[11]. Despite animal research demonstrating the presence of progesterone receptors (PRA and PRB) in brain regions involved in cognition, little is known about their location in the human brain[10, 12]. Natural experiments, or circumstances that lead to natural variations in hormones,[13, 14] and relatively recent methodological developments in neuroimaging (e.g., accessibility to magnetic resonance imaging, MRI), endocrinology (e.g., availability of estradiol salivary assays)[15], and computation (e.g., power to analyze multimodal data sets) combine to facilitate investigations into the role of ovarian hormones in cognitive neuroscience.

When studying ovarian hormones, it is important to consider the nature of effects. Broadly, sex hormone effects on the brain and behavior can be organizational or activational[16, 17]. Organizational effects generally concern hormone exposure during sensitive periods of development; they are permanent and have historically been tied to sexual differentiation, in that hormone-influenced brain circuits persist throughout life and are important for sex-typed behaviors. Activational effects generally concern transient exposure,

in which sex hormones stimulate brain circuits (and the sex-typed behaviors they subserve) only when they are present.

Focus of review

The goal here is to review recent work (i.e., within the last five years) on the role of ovarian hormones in shaping cognitive brain structure and function by utilizing five natural experiments across the human lifespan: puberty, the menstrual cycle, hormonal contraceptive use, menopause, and menopausal hormone therapy. The experiments are depicted by black lines in Figure 1, showing relative changes in ovarian hormone levels over a month (see inset) and across years. Each natural experiment is thought to have activational effects, and the majority of the literature considers these. Several experiments may also have organizational effects (indicated by stars). Although the greatest evidence for organizational effects of sex hormones on the human brain comes from androgen exposure during prenatal development[14], it is increasingly clear that pubertal estrogens are organizational[18, 19], and emerging longitudinal data from other natural experiments provocatively suggest that ovarian hormones may have organizational effects at other points in women's lives.

The five natural experiments are considered, in turn, in what follows. First, ovarian hormone variations that characterize each natural experiment are described. Next, associated changes in cognitive performance are briefly presented for contextualization. Finally, cognitive neuroscience studies on brain structure and function, including connectivity, in relation to the variations are synthesized; because the aim of this special issue is to communicate recent trends in the field, work within the past five years is examined in detail, following a brief synthesis of early studies to convey the state of the science through 2014. The review closes by integrating findings across natural experiments, noting limitations and highlighting promising areas for future work.

Throughout the review, the emphasis is on recent cognitive neuroscience studies conducted in typical samples with relatively sound methodology. This focuses the scope of the review, minimizes potential confounding effects of patient status and related physical and mental symptoms, and reduces the likelihood of presenting non-replicable results; primarily affective or social neuroscience studies are beyond the scope of this review.

Puberty

Puberty is characterized by stark increases in the production of sex hormones, and it marks the beginning of transformative adolescent changes in neurocognition[20, 21]. There are three axes of pubertal development: growth concerns overall changes in physiology, adrenarche concerns the maturation of the androgen-secreting adrenal glands, and gonadarche concerns maturation of the estradiol- and progesterone-secreting ovaries in girls[22]. Gonadarche typically occurs between the ages of 10 and 18 years, and is evident in breast development and menarche, or the first menstrual bleeding. Adolescent ovarian hormone influences on cognitive brain structure and function can be revealed through studies of the status or timing of gonadarche. Most work concerns the activational effects of pubertal status, or where an individual is in the process of puberty. There is, however, emerging work on pubertal timing, or when a girl develops compared to her same-age peers. Pubertal timing may capture organizational effects. A recent hypothesis posits that the brain has declining sensitivity to sex hormones throughout childhood and adolescence, such that females who mature early have greater effective ovarian hormone exposure than those who mature late, and thus, are most sex-typed in their behavior and cognition.[23]

Cognitive performance

Research on links between pubertal ovarian hormones and cognition is scant. Despite evidence for cognitive improvements across adolescence[24, 25], the limited available data provide little indication of an association between puberty in girls (status, timing, or estradiol levels) and traditional domains, such as memory, verbal fluency, and spatial skills[26-28]. There is some theoretical and empirical evidence, however, for pubertal hormone contributions to the adolescent increase in risk-related decision-making[29, 30]. Unfortunately, most studies on puberty and cognition are cross-sectional, so future longitudinal work with large samples is needed.

Early findings

Early work on puberty and neurocognition concerned pubertal status and focused on the role of testosterone[31, 32]. Some work on estradiol and brain structure was conducted, though. Findings suggested that increases in the ovarian hormone are linked to gray matter decreases, including in the prefrontal cortex[33], and also to decreases in the integrity of white matter tracts[34]. Results, however, were mixed across studies. For instance, there was (and continues to be) particular interest in ovarian hormones and hippocampal structure and function, given estrogen's contributions to hippocampal synaptogenesis in animals[17], but pubertal estradiol has not been consistently linked to these volumes[33, 35]. The discrepancies are not surprising, given the small sample sizes (i.e., $n < 50$ girls) of early studies.

Early work on pubertal estradiol and brain function is also limited. A study showed positive links with activity in monetary reward processing regions known to be sensitized during adolescence, such as the striatum and medial PFC, but results did not reach traditional levels of significance in the small sample ($n = 30$ girls)[31]. Social-emotional decisions are also sensitized during adolescence, and a study showed a positive link between estradiol and temporal cortical activity in a related task, but again, the sample was small ($n = 42$ girls)[36].

Recent findings

Most research on puberty and neurocognition continues to focus on testosterone and on pubertal status in domains strongly yoked to adolescent development (e.g., reward processing), with little to no consideration of pubertal timing and basic cognitive functions. Nonetheless, recent work with ever-increasing levels of rigor suggests that ovarian hormones, particularly estradiol, are indeed unique contributors to neurodevelopment.

Cognitive brain structures. There are several recent reviews on puberty and structural brain development[37-39], with two providing comprehensive lists outlining relevant studies[37, 39]. In these reviews, advanced pubertal status is consistently implicated in the gray matter reductions typical of adolescent brain development, such that estradiol increases in girls are linked to cortical thinning and decreased gray matter densities. There is little empirical evidence for estradiol influences on white matter development at puberty, though, as testosterone appears to underlie the change[37, 39], aligning with sex differences in white matter volume favoring males[3, 38]. Findings continue to be inconsistent regarding the hippocampus, with advanced pubertal development in girls linked to hippocampal volumes in one recent study[40], but not in another[41]. Such inconsistencies can be attributed to a variety of methodological issues (e.g., varying sample sizes and study designs, detection of nonlinearities in developmental trajectories, and challenges in disentangling pubertal status and age during adolescence), especially given consistent links between estrogen and the hippocampus found in other natural experiments (reviewed below).

There is also some emerging work on pubertal timing and cognitive brain structures that is consistent with an adolescent brain reorganizational hypothesis: Early timing is associated with greater integrity (i.e., lower mean diffusivity) of frontal white matter tracts in

early adulthood[42]. Thus, ovarian hormones may facilitate frontal maturation, with effects stronger and persistent for those with early (versus late) pubertal timing.

Cognitive brain function. Although recent reviews consider pubertal development and brain function during cognitive performance—and even include comprehensive lists detailing relevant studies—there has been little explicit focus on ovarian hormones[38, 39]. Most applicable research concerns estradiol's role in reward processing. Expanding on early work[31], some studies have linked increased activity in reward processing regions, such as the nucleus accumbens (part of the ventral striatum), to decreased risk-taking in girls[43], implicating estradiol in observed sex differences in risk aversion[3, 44]. There is some suggestion that the neural circuits underlying reward processing differ for monetary and social cues, as activity in the insula was uniquely linked to social reward processing and estradiol levels in adolescent girls[36, 45]. However, recent work has reported opposing[46] and null effects[47]. Inconsistent reports are likely due to the continued use of small samples, the confounding of pubertal status and age in cross-sectional studies, region-specific effects that depend upon connectivity within striatal subregions[46], and menstrual cycle fluctuations in post-menarcheal girls. Nonetheless, estradiol seems to contribute to reward processing, and this is expected based on the hormone's stimulations of and interactions with dopamine[48, 49]. Future work with larger samples that incorporate advanced metrics of neural connectivity and appropriate methods for considering menstrual cycle fluctuations in estradiol will be illuminating.

Summary

There is accumulating evidence suggesting that activational effects of ovarian hormones, particularly estradiol, contribute to frontal gray matter reductions in adolescence and likely play a role in reward processing. There is also emerging evidence suggesting that

activational effects of estradiol contribute to social processing, and very early indications that organizational effects of ovarian hormones may be important for frontal cortical development. More work on pubertal timing is needed. This will require retrospective studies of pubertal timing in adults, or ideally, longitudinal studies that span puberty and young adulthood (to test permanence of outcomes)[50, 51]. Future work investigating progesterone and co-occurring menstrual cycle effects on brain structure and function during puberty and linked to basic cognitive functions is also needed.

Menstrual cycle

The typical menstrual cycle is 28 days long, with normal variation ranging from 22 to 35 days[52, 53]. Menstruation is generally considered the beginning of the cycle, which is divided into two phases – follicular and luteal – that are defined by estradiol and progesterone levels. The follicular phase begins after the first day of menstruation and is characterized by initial low levels of both estradiol and progesterone followed by rising estradiol. The late follicular phase (i.e., the second week of the menstrual cycle) is characterized by rapid increases in estradiol that surge to a peak and trigger the release of luteinizing hormone (LH). Ovulation occurs shortly after the peak of estradiol and subsequent release of LH (~1 day after both)[54]. The luteal phase begins after ovulation and is characterized by a sharp decrease in estradiol that settles at moderate levels while progesterone begins to rise and reaches its peak approximately midway through the phase. The latter part of the luteal phase sees both estradiol and progesterone decline as menstruation approaches (i.e., pre-menstrual phase) and the cycle begins again. The focus here is on naturally cycling healthy participants, which provides the clearest test of activational effects, as patient studies can be confounded by disease processes and medication. Figure 2 presents empirically-informed simulated data showing estradiol and progesterone levels across the menstrual cycle for individual women.

Notice that each woman is different with respect to the length of her cycle and her patterns of hormone fluctuations across phases.

Cognitive performance

A recent critical review of the literature suggests there are few replicable differences in cognition across the menstrual cycle or as a function of ovarian hormones[10]. Based on research and theory regarding sex differences in spatial and verbal abilities, however, there have been a number of studies suggesting that spatial[55] and numerical[56] abilities are enhanced when hormones are low (i.e., early follicular phase), whereas verbal and related memory abilities are enhanced when hormones are high (i.e., late follicular, mid-luteal phase)[57, 58]. Extant work is limited, however, by low power and variability in definitions of menstrual cycle phases. Nonetheless, consistent with the review[10], neuroimaging studies provide evidence for menstrual cycle and hormone effects on neural structures and function underlying cognition, especially verbal abilities. It may be that neural measures are more sensitive to the subtle effects of hormonal milieu than is behavioral output, or that brain structure and function compensate for ovarian hormone variations.

Early findings

Early studies of menstrual cycle effects on cognitive brain structures and function are informative, but limited by small heterogeneous samples (e.g., including patients with premenstrual dysphoric disorder)[59] and differences in when scans were performed during the cycle. Nonetheless, the late follicular phase (i.e., high estradiol) has been associated with relatively larger hippocampi as well as relatively smaller basal ganglia and anterior cingulate cortices (ACC)[59, 60], with the hippocampi and basal ganglia playing a role in memory and the ACC representing a core hub involved in the adaptive control of behavior and learning[61]. An

inverse relationship between ACC volume and estradiol in the mid-luteal phase has also been reported[60].

There were also early functional studies of menstrual cycle effects on cognitive processes. Studies are heterogeneous and effects are mixed; however, there seems to be a consistent effect of estradiol levels in the frontal cortex across a variety of verbal memory and fluency tasks[62-65], with some evidence that progesterone is also involved[64]. Interestingly, neural findings were generally not related to cognitive performance. In a particularly sophisticated early study, however, there was evidence for the modulation of verbal working memory and dorsolateral PFC activity by a combination of estradiol and the catechol-*O*-methyltransferase (COMT) genotype—related to dopamine release—consistent with a role for estradiol in frontal cortex–mediated verbal memory functions[57]. Finally, despite several investigations, there is little consensus stemming from early studies on menstrual cycle effects on spatial abilities[63, 66, 67]: Neural processes do seem to be modulated by the menstrual cycle in temporal, parietal, and frontal regions, but methodological limitations challenge the identification of converging conclusions.

Recent findings

Recent findings are also limited in number and methodologically heterogeneous; however, they point to menstrual cycle changes in a number of brain regions, with a particular focus on the hippocampus[68]. Key studies from the past five years are summarized in Table 1.

Cognitive brain structures. The hippocampus is implicated in a number of important memory functions[69]. Two recent studies reported increased hippocampal volumes during the late follicular phase when estradiol levels are rising and progesterone is low[70, 71]. One demonstrated a direct positive association between estradiol levels and hippocampal volumes[71], whereas the other found a positive association between estradiol and

parahippocampal volumes[70]. Although these regions are close in proximity, they are distinguishable with regard to location and function[72]. An intensive longitudinal single-subject design further confirmed a positive association between estradiol and hippocampal volumes, though[73].

The basal ganglia have also been of interest because they are involved in related, yet distinct, memory and learning mechanisms tied to the hippocampus[74]. Again, there is limited evidence for menstrual cycle effects; however, a recent study found that basal ganglia volumes are smaller when estradiol levels are relatively higher[71], opposite the pattern observed for the hippocampus. In this study, participants were compared in the late follicular phase (when estradiol is high and progesterone is low) and the mid-luteal phase (when estradiol is falling but progesterone is high), but basal ganglia volumes were only positively correlated with progesterone levels. Together, these findings reveal the significance of progesterone and its interaction with estradiol.

Finally, a number of other regions have been reported to change in size across the menstrual cycle and demonstrate associations with hormone levels[68]. These include the fusiform, other temporal regions, the medial frontal cortex, and the insula. Many are adjacent to those reported above and therefore might not show unique effects across the menstrual cycle, but rather, reflect effects on broader memory and learning circuits that could be revealed with future connectivity analyses.

Cognitive brain function. A recent longitudinal study of 36 women extends earlier findings showing a relation between increased levels of estradiol and hippocampal function[75]. Interestingly, however, this relation appeared stronger in a spatial navigation than verbal fluency task. Moreover, there were relations between higher progesterone and greater caudate and dorsolateral PFC activity. These also appeared stronger during a spatial than verbal task, potentially reflecting differential statistical power between the tasks. Beyond verbal and

spatial processing, recent work on menstrual cycle effects on cognitive brain functions concerns cognitive control and resting state functional connectivity. Regarding cognitive control, effects are mixed. One study reported greater no-go related activity in PFC regions during the late follicular compared to the late luteal/pre-menstrual phase, suggestive of a relation between higher estradiol and performance monitoring PFC activity, despite no links to behavior[76]. In direct contrast, another study found increased activity in the ACC and greater functional connectivity within the fronto-parietal attention network across go and no-go trials during the menstrual/early follicular (i.e., low levels of estradiol and progesterone) and late follicular (i.e., rising estradiol and low progesterone) phases compared to the mid-luteal phase (i.e., moderate levels of estradiol and high levels of progesterone), but ACC effects were only detected after loosening the significance threshold[77]. The discrepant findings likely reflect the presence of small effects that are modulated by individual differences (e.g., in cyclicity). A particularly strong recent study reported increased ACC activation to negative feedback in the mid-luteal (i.e., moderate levels of estradiol and high levels of progesterone) compared to the late follicular (i.e., rising estradiol and low progesterone) phase during completion of a reinforcement learning task[78], suggesting a progestagenic effect. Behavioral performance also indicated that this increase in feedback-related ACC activation was accompanied by increased avoidance learning, again pointing to a role for progesterone.

Regarding resting state functional connectivity, studies generally fail to detect effects of menstrual cycle phase on connectivity metrics of whole networks, such as the hallmark default mode network (DMN). Rather, they report changes in how networks are related to particular nodes, or regions, as a function of menstrual cycle phase. For instance, there is some suggestion that regions within the DMN appear more connected when hormones are low (early follicular phase)[79, 80], whereas regions within control networks appear more

connected when progesterone or both progesterone and estradiol are high (mid-luteal phase)[81, 82]. But this is not always the case, as greater control-related connectivity in the early follicular phase (i.e., low hormones) and complex patterns of correlations between estradiol and progesterone in several different networks, including the DMN, have been reported[79, 83]. Moreover, two studies failed to find any discernable menstrual cycle effects on the DMN or control networks[84, 85].

Summary

Extant research on activational menstrual cycle effects on cognitive brain structures and function provides preliminary insights into the role of ovarian hormones in cognitive neuroscience. Structural work points to the hippocampus, basal ganglia, and ACC as regions of interest. Functional work has further produced evidence for ovarian hormone contributions to frontal activity during verbal processing and memory tasks. Resting-state connectivity studies are particularly problematic as they do not report any menstrual cycle effects on intrinsic connectivity of networks per se, but changes in how nodes cohere with broader network activity point to the possibility of interesting effects that can be examined in future work.

Hormonal contraceptives

Hormonal contraceptives consist of a synthetic progesterone (i.e., progestin), and in combined formulations, a synthetic estrogen. These exogenous hormones dampen the production of endogenous estradiol and progesterone and control ovulation, not only making them effective forms of birth control, but also leading to insights about the role of ovarian hormones in cognitive brain structures and function. Hormonal contraceptives have various routes of administration, including oral, transdermal, and intrauterine. Here, the focus is on

oral contraceptives (OCs) because they are common, and will be used by over 85% of women in the United States for at least five years of their life[86]. It is important to note, however, that OCs are heterogeneous. Most contain 21 active pills followed by 7 placebo pills (instigating menstruation), but some formulations have longer or shorter pill phases. OCs also vary in dose, and most contain ethinyl estradiol, and have progestins with different hormone derivatives; for instance, some pills have progestins with androgenic activity while others are anti-androgenic[87, 88]. Most research concerns the activational effects of OCs, although organizational effects are theoretically possible.

Cognitive performance

There is increasing evidence suggesting that OC use influences cognition. Verbal memory seems to be most consistently facilitated by all OCs[89], whereas spatial ability is only enhanced in users of pills with androgenic progestins[90, 91]. There is also indication that OC use decreases verbal fluency[92]. Most relevant studies are cross-sectional and conducted with homogenous and privileged populations (e.g., White, North American college students with health insurance), however, and should therefore be interpreted with caution in this nascent stage of research.

Early findings

Early work suggested that users (compared to naturally cycling women) have larger PFC and ACC volumes as well as larger hippocampal, parahippocampal, fusiform, and other temporal regional volumes[93]. This was supported by the lone longitudinal study in this area, showing larger mid-frontal gyri in users of OCs compared to naturally cycling women[60]. Effects even extended to differences between pill phases, such that mid-frontal gyri, ACC, and insula were larger during the active compared to placebo phase, although effects were

small[60]. Moreover, an early functional study of OC users compared to women in their menstrual/early follicular phase showed greater right superior temporal and left inferior frontal cortex activation during a verbal processing task[94]. Although samples are small and OC formulations were not reported in these studies, they tentatively suggest that exogenous hormones modulate hippocampal and frontal volumes and play a role in verbal neurocognition, consistent with menstrual cycle research.

Recent findings

Although there is limited recent work, the emerging evidence for OC effects on cognition and the huge number of women using OCs makes it critical to begin to understand neural mechanisms. Extant findings are summarized in Table 1.

Cognitive brain structures. Work on OC effects on cognitive brain structures speaks to potential androgen effects in the context of ovarian hormones. For example, in a more recent cross-sectional study, women using pills containing anti-androgenic progestins were compared to those using pills containing androgenic progestins and naturally cycling women during their menstrual/early follicular phase[95]. Women taking anti-androgenic pills had larger parahippocampal and fusiform volumes relative to naturally cycling women, potentially reflecting heightened estrogenic activity in these pill users. But, these results do not replicate early findings (mentioned above) of larger ACC or hippocampal volumes in OC users in neither cross-sectional[93] nor longitudinal[60] designs. In fact, women using pills with androgenic progestins actually demonstrated smaller middle and superior frontal gyri than naturally cycling women[95]. These findings mark the complexities of studying OC effects, which likely involve transactions among ovarian–and other sex–hormones.

Cognitive brain function. Despite a lack of performance differences between OC users and naturally cycling women during two number processing tasks, a recent study

reported reduced fronto-parietal activation in OC users compared to women in their follicular phase and greater medial PFC and inferior parietal activation in OC users compared to women in their mid-luteal phase[87]. Results are preliminary, though, due to the small sample, lack of information on OC formulation, and limited contextualizing research on the neural correlates of number processing.

Resting state functional connectivity studies in OC users have also produced mixed results, and like in menstrual cycle studies, none find changes in overall network connectivity. Some studies report no differences between women using OCs and naturally cycling women[84], whereas others report conflicting effects. For instance, compared to naturally cycling women, there is indication that women using OCs have reduced connectivity in DMN regions[79], but that women using androgenic OCs have greater connectivity in different DMN regions[82]. There is similar confusion between studies when comparing active versus placebo phases in the fronto-parietal network.

Summary

Research concerning OC effects on cognitive brain structures and function is just emerging. Samples are small and vary in OC formulations, which often go unreported. Although there is some indication of exogenous estradiol and progestin modulation of frontal and hippocampal regions, emerging findings suggest that interactions among ovarian hormones and androgens may also be important. Future systematic work is needed in this area, including longitudinal work that distinguishes between activational and organizational effects of OCs. Given the widespread use of OCs, this work is feasible and carries significant potential and health implications.

Menopause

Menopause, or the final menstrual period, is marked by drastic reductions in estradiol and progesterone levels due to the cessation of ovarian function. Natural menopause typically occurs around age 51 when there has been no menstrual period for 12 consecutive months[96]. Induced menopause, which result from treatments, such as oophorectomy (i.e., removal of the ovaries), can occur abruptly. The focus here is on natural menopause due to possible confounds in clinical patients. The menopausal reduction in ovarian hormones, particularly estradiol, is thought to contribute to risk for cardiovascular disease and osteoporosis as well as to vasomotor (e.g., hot flashes) and urogenital (e.g., vaginal dryness) symptoms[97], begging the question about the activational versus organizational effects of ovarian hormone decline at menopause.

Cognitive performance

Along with physiological symptoms, menopausal women also often report cognitive decrements[98], although empirical evidence is mixed[99]. Overall, there is suggestion that aspects of memory, particularly verbal memory, are negatively impacted by menopause, and that there are decrements in processing speed, attention, and verbal fluency. Effects, if they indeed exist, are likely small, and perhaps time-dependent, with some reports suggesting they are only present for the four years surrounding menopause (i.e., peri-menopause)[96, 100] or greatest after menopause (i.e., post-menopause)[101, 102]. Inconsistencies are likely due to sample characteristics (e.g., age-associated cognitive decline or education) and study methods (e.g., cognitive domains assessed and covariates) as well as unmeasured individual differences (e.g., stress).

Early findings

There is not a large corpus of research on menopause that illuminates the ways in which ovarian hormone decline may be linked to cognitive brain structures and function. There was an early report of increased frontal and temporal activation during verbal tasks across the menopausal transition, with neural activation inversely related to estradiol levels[103]. Verbal decrements accompanied this functional increase, so findings suggest links among decreased estradiol, impaired verbal cognition, and increased recruitment of frontal regions.

Recent findings

There is, however, some recent neuroimaging research on menopause. As was the case for the menstrual cycle and OC use, this work has focused on the hippocampus and, increasingly, the PFC, given the possible verbal and executive function impairments that accompany menopause[99]. Key studies from the past five years are summarized in Table 2.

Cognitive brain structures. There is emerging evidence for structural decrements associated with menopause, and some suggestion that they are related to declining estradiol levels. For instance, compared to pre-menopausal women, post-menopausal women have lower gray matter volumes in the supplementary motor area and other frontal (e.g., inferior frontal gyrus) and temporal (e.g., superior temporal gyrus) regions, and across women, volumes were positively correlated with estradiol[104]. Although pre- and post-menopausal women also differed in hippocampal volume, findings did not withstand corrections for age[104]. In other work, though, hippocampal volume was positively linked to verbal memory in post-menopausal women[105], providing early indication that gray matter reductions not only reflect estradiol decline, but also have implications for cognition. Moreover, among peri- and post-menopausal women, a positive association has been reported between physiologically-monitored hot flashes associated with estrogen decline and white matter hyperintensities[106],

or lesions thought to reflect cardiovascular insults, which increase at menopause[96, 97]. Cognition was not studied, but since white matter hyperintensities appear to be related to cognitive impairments[107, 108], it is reasonable to hypothesize that they contribute to cognition in menopausal women.

Cognitive brain function. There is also evidence for changes in brain function associated with the menopause during verbal tasks and the cognitive control of emotion processing. With respect to verbal processing, hippocampal function seems to be altered among pre-, peri-, and post-menopausal women, with post-menopausal women showing the least hippocampal activity during verbal processing and the least hippocampal deactivation during verbal working memory; in both cases, hippocampal activity was related to estradiol[109, 110]. The difference between inverse hippocampal activation and attenuated hippocampal deactivation can likely be explained by varying task demands and hippocampal connectivity. For instance, post-menopausal women had increased connectivity among the bilateral hippocampi during verbal processing[109]. They also exhibited increased dorsolateral PFC activity during verbal working memory, and only for these post-menopausal women did connectivity between the dorsolateral PFC and hippocampus predict task performance[110]. With respect to cognitive control during emotion decision making, specifically the identification of negatively-valenced images, there is evidence for increasing activation across menopause, such that post-menopausal women uniquely engaged the PFC, posterior cingulate, and temporoparietal junction[111]. It is interesting to note, though, that menopausal status did not influence activation in traditional emotion processing regions in the limbic system.

Finally, there is early indication that cognitive processes reflected in resting state connectivity are related to ovarian hormones at menopause. For instance, in post-menopausal women, subjective cognitive complaints, but not an objective memory test, were positively

linked to executive network connectivity, indexed by connectivity with a dorsolateral PFC seed region[112]. Identifying links only with subjective measures is perplexing, and all women were post-menopausal, so study results do not speak to the menopausal transition per se. Furthermore, connectivity within the DMN, including the hippocampus, was positively linked to physiologically-monitored hot flashes, potentially suggesting that estradiol decline contributes to DMN hyperactivity, which has negative consequences for psychological well-being[113]. It is not clear, however, how this finding aligns with a growing literature on sex differences in DMN connectivity, in which women are consistently shown to have greater connectivity than men[114]. Based on this, ovarian hormones would be expected to facilitate connectivity, and thus, menopause to lead to reduced DMN connectivity. To resolve these discrepant findings, future work should use larger samples and consider the potentially unique role of the hippocampus within the DMN.

Summary

There is an emerging literature on menopause that suggests ways in which ovarian hormones, particularly estrogen declines, contribute to cognitive brain structures and function. There is evidence of estradiol-linked gray matter decline in the frontal lobe and of altered hippocampal activation during verbal tasks across the menopausal transition. There are also provocative findings, including menopause-associated increases in white matter hyperintensities and altered cognitive processing during emotion identification and in resting state networks. Beyond the obvious need for replication of early findings in larger samples, there are also significant opportunities for future investigations utilizing longitudinal methods (as most extant work is cross-sectional) and for the differentiation between activational and organization effects.

Menopausal hormone therapy

Because of the side effects associated with menopause, many women use hormone therapy to ease the transition, creating natural experiments for the administration of exogenous hormones. Menopausal hormone therapy (MHT) comes in several forms; the focus here is on oral and transdermal administrations thought to have systemic effects, as other administrations (e.g., vaginal creams) are localized. Women with natural menopause will likely use MHT consisting of combined estrogens and progestins; estrogens can be estradiol or conjugated equine estrogens, and progestins vary in their hormone derivatives (as in hormonal contraceptives).

MHT has a checkered history: early work conducted as part of the Women's Health Initiative (WHI) randomized controlled trial initially suggested an increased risk for cardiovascular disease among MHT versus placebo users, so the trial was stopped early [115]. There was also evidence for cognitive and neurological deficits for WHI participants using MHT[116]. Although it is not clear if findings depend upon characteristics of the sample (e.g., weight) or MHT formulation (i.e., conjugated estrogens with an antiandrogenic progestin), it is noteworthy that adverse outcomes involved older (above age 65), post-menopausal women. Beyond these risks, there is now consensus that MHT also has some benefits (e.g., alleviates vasomotor symptoms and helps prevent bone fractures), especially during a critical window of menopause[96, 97]. Specifically, peri-menopausal MHT for about five years in healthy women under age 60 is recommended with careful consideration of other risks[96, 97].

Cognitive performance

Although MHT is not recommended solely to alleviate cognitive detriments possibly co-occurring with menopause[100], a relatively long history of work makes clear that it facilitates the maintenance of some aspects of cognition in peri-menopausal women. Verbal

memory is consistently seen to be maintained or even enhanced by estradiol treatment, and there is indication of small, positive effects of MHT on learning and processing speed as well as reduced dementia and even Alzheimer's disease risk, although debate surrounds the latter[97, 100, 117, 118]. Effects vary, however, with MHT type and timing, and there are individual differences (e.g., time since and neurocognitive health prior to menopause)[116].

Early findings

Early research on MHT suggested that ovarian hormones indeed contribute to cognitive brain structures and function. As was the case for menopause, most work focused on the frontal lobe and hippocampus[119]. For structure, there were several reports of greater gray matter volumes in MHT users versus non-users, including in the frontal and temporal cortices as well as the hippocampi[120-123], but they were inconsistent concerning comparisons between current and past users, effects of age, and associations with duration of MHT. There were also several contradictory reports for MHT effects on the same exact regions[124-126]; the reports with positive effects were limited by small sample sizes and employed relatively young samples (post-menopausal women in their 60's), whereas reports of volume decrements linked to MHT employed larger, older samples (in their 70's). In fact, one report was based on the Women's Health Initiative Memory Study (WHIMS-MRI)—an ancillary to the WHI study; thus, it was large (n = 1403), but participants were heterogeneous in MHT formulation (with some using estrogen only and others using combined estrogen + progesterone therapies) and of advanced age (71–89 years), with scanning conducted years after MHT ended. Thus, some forms of MHT likely have small effects on frontal and hippocampal volumes depending upon age, duration, and time since cessation of treatment.

For function, early reports generally converged across study designs (e.g., user versus non-user comparisons, clinical trials, and repeated measures investigations). Utilizing positron emission tomography, there was consistent evidence for greater cerebral bloodflow

in MHT users versus non-users[127], particularly in the frontal lobe and hippocampus during memory tasks[128]. Aligning with this, evidence from functional magnetic resonance imaging (fMRI) studies showed greater activation in frontal and parietal cortices as well as the hippocampi (among other regions) during spatial, visual, and verbal working memory tasks[129-133]. Interestingly, however, the increased activation associated with MHT has not consistently been related to working memory, as several studies reported no task performance differences in MHT users versus non-users[130, 132].

Recent findings

Likely due to the consistency of past work on MHT and working memory-related neural activation, most recent cognitive neuroscience research has focused on clarifying the inconsistent effects of MHT on cognitive brain structures, and on extending effects of brain function to domains beyond memory and to ovarian hormone mechanisms. Extant studies are summarized in Table 2.

Cognitive brain structures. There are recent reports of decreased frontal gray matter in MHT users versus non-users[134-136], and several studies have focused on the hippocampus, with one showing a positive short-term (i.e., 3-month) treatment effect of relatively high doses of estradiol compared to low doses and placebo[137], but two others reporting null effects when comparing current, past, and non-users[105, 134]. The pattern of findings could reflect MHT formulation (e.g., studies reporting null effects grouped users of estrogen and combined therapies), or neural plasticity occurring around the MHT transition. Congruent with the latter, follow-up data from the longitudinal WHIMS-MRI (with scanning occurring several years after MHT cessation) suggested reduced hippocampal volumes in MHT versus placebo users[135], although there was not significant decline from 1–3 to 6–7 years post-treatment.

There are also conflicting reports of enlarged ventricular volumes, reflecting brain aging and cognitive decline[138], and increased white matter hyperintensities in MHT, with some studies finding effects[139], and others not[135, 136]. Again, discrepancies may be due to transitional versus persisting effects of MHT, as studies reporting null results were based on longitudinal WHIMS-MRI data collected several years after MHT cessation, and a key study reporting effects was a long-term (i.e., 48-month) randomized trial. Furthermore, a 3-year follow-up to this trial reported that ventricular volumes no longer differed among groups, but that white matter hyperintensities did[140], suggesting that aging effects (reflected in ventricular volumes) equalize over time. Questions remain regarding MHT effects on white matter hyperintensities, perhaps indicating that effects are present but small or that they are moderated by risk factors, such as diabetes status[141], individual differences in cognitive ability prior to MHT[135], and estrogen receptor genotype[134]. As in early studies, there are few direct associations between brain structure and cognition in MHT users[139, 140].

Cognitive brain function. Studies on verbal processing confirm past work in finding increased frontal activation in MHT (grouping estrogen and combined) users versus non-users[142]. Ovarian hormone mechanisms underlying this and previously-reported working memory effects have also been explored in a short-term (i.e., 90-day) randomized crossover trial of estradiol and progesterone treatment in peri-menopausal women[143]. As expected, estradiol treatment was linked to increased frontal activation during verbal processing. Novel links for progesterone were also revealed, such that it was inversely associated with frontal activation during verbal processing, but with increased frontal and hippocampal activation during working memory, potentially suggesting that previous findings of MHT treatment on increased neural activation[130, 133] were not due to estradiol alone, but due to progesterone or the combined effects of the hormones.

Other recent studies have considered brain activity during cognitive control and reward processing using cross-over designs in which the same peri- or early post-menopausal women participated in MHT and placebo conditions. Although intriguing and strengthened by the use of repeated testing, results require replication, as samples were small ($n < 15$). During a cognitive control task, combined MHT was associated with greater frontal activation, particularly in the PFC and ACC[144]. The increased activation did not reflect performance differences between study conditions, though. During a reward processing task in the same sample, MHT was also associated with greater putamen and ventromedial PFC activation, with estradiol levels during MHT positively linked to putamen activity[145]. These results complement those seen during puberty, with ovarian hormone increases linked to striatal and ventromedial PFC activation[31], and with emerging evidence for estradiol's interplay with dopamine[57].

Summary

There is a relatively large literature on MHT effects on cognitive brain structures and function. Current research suggests that peri-menopausal MHT may positively contribute to cognition. Unfortunately, most neuroimaging research is misaligned with this because it utilizes data from post-menopausal women or short-term placebo-controlled trials. Thus, more work with peri-menopausal samples is needed. Nonetheless, the extant literature has focused on MHT effects on the frontal lobes and hippocampi. Functional studies are quite consistent in showing that MHT increases activation in these regions during verbal and working memory tasks, with intriguing evidence that progesterone (along with estrogen, which has been the emphasis) contributes to relations, and that effects are modulated by individual differences. Structural studies are more mixed. Some effects (e.g., ventricular enlargement) seem to be activational (i.e., only present when women are using MHT),

whereas others (e.g., reduced frontal volume) are arguably organizational (i.e., persist after MHT has ended).

Integration

Across natural experiments—puberty, the menstrual cycle, hormonal contraceptives, menopause, and MHT—there is evidence for ovarian hormone contributions to women's brain structure and function. Some effects appear to be consistent across experiments. For instance, estrogen plays a role in frontal and hippocampal gray matter volumes, estrogen and progesterone influence fluctuations in the PFC and ACC during cognitive tasks, and there is a unique role for estrogen in reward processing. These findings likely reflect general mechanisms, properties, or actions of the hormones that are expected to generalize broadly, including to men. Other effects emerge in some natural experiments, but not others. For instance, estradiol is inversely related to cortical thickness in puberty, but positively related to frontal gray matter in the other natural experiments, and androgen interactions seems to be important during puberty and in OCs. These findings likely reflect hormone interactions with typical age-related neural processes (e.g., in adolescence or aging), differences between endogenous and exogenous hormones, or regional effects in the brain.

Findings must be interpreted in light of their actual links to cognition. Several recent studies do not explicitly measure cognition (see Tables 1 and 2), severely restricting their implications for cognitive neuroscience. Among studies that consider cognition, most report no neuroendocrine links to performance; in other words, neural differences associated with ovarian hormones are not apparent behaviorally. Thus, neuroendocrine effects might reflect compensation or equifinality, in that there are multiple mechanisms leading to the same outcome[3, 146, 147]. This may also suggest that ovarian hormones mediate, but do not determine, neurocognition.

Considerations and limitations

Findings must also be considered in light of study designs. Some samples are small. This leads to concerns that reported effects actually are false positives with inflated effect sizes[148]. Fortunately, awareness of the perils of small samples is rising, and recent publications have increased power compared to early work (see several studies in Tables 1 and 2). Moreover, neuroimaging data from large-scale studies with information on ovarian hormones are being collected and made publicly available, facilitating future rigorous research; for example, puberty can be examined in the 10-year Adolescent Brain Cognitive Development study[149].

Sample characteristics are also vital to consider when evaluating studies linking ovarian hormones to cognitive brain structures and function. Pubertal status and timing are often confounded during adolescence. Measurement is paramount in menstrual cycle studies; self reports are inaccurate and even hormone monitoring must be done across several cycles to ensure precision. OC formulations (e.g., progestin androgenicity) and length of use matter; ignoring either can bias results. Age must be carefully considered in menopause research; it can reflect typical cognitive decline. Hormone constituents (e.g., conjugated equine estrogens or estradiol with or without a progestagen) and sample characteristics are important in MHT studies; formulations vary and wealthy, educated women tend to self-select into treatment.

Furthermore, inferences from natural experiments of ovarian hormones are tightly yoked to study designs. Cross-sectional designs capture neural differences associated with hormone levels or milieus across groups (e.g., pre- versus post-menopausal women) or time (e.g., follicular versus luteal phase). Potential quadratic or threshold effects are often missed, which are problematic since hormone mechanisms are likely nonlinear and interactive[150-152]. Generalizability is also limited to particular groups (e.g., OC users of one formulation), but

this is seldom reported. Longitudinal designs (with more than two measurement occasions) overcome some of these limitations. They capture hormone change and permit the examination of within-person nonlinear trends across time. Unfortunately, they are rare (though most common in puberty and menstrual cycle research). They require significant resources, and given the nascent stage of the field, may not provide insights for many years. Moreover, they provide the ability to examine both within-person changes across time and between-person differences across the entire study, but many extant studies fail to disentangle these effects, and thus, may reach inaccurate or incomplete conclusions; person-centered effects most directly inform hormone changes over time.

Beyond broad distinctions of study designs, inferences are also dependent upon the hormone operationalizations within a given study. Different approaches can be used within a single natural experiment (e.g., randomized trials, comparisons of naturally occurring groups, and follow-up studies in MHT). Each affords different inferences, so it should not be surprising if effects do not converge across approaches because the hormone assessments reflect different neuroendocrinological processes (e.g., randomized trials reflect short-term transitions, while follow-up studies reflect long-term effects). Thus, it is vital for future studies to specify the nature of hormone influences on the brain. One way to do this is to consider whether ovarian hormone effects—as tested within a given study design—are activational or organizational. Most effects are activational, but some (e.g., those linked to the menstrual cycle) may be solely activational, while others are also organizational. Organizational effects were once thought to occur only during prenatal development[16, 17], but emerging evidence that they also occur during puberty[18, 19] begs the question of whether they are present during any neural transition, as indicated (by stars) in Figure 1.

Future directions

It is an exciting time to study the cognitive neuroscience of ovarian hormones. The importance of sex differences and the hormonal mechanisms that contribute to them has been realized by funding agencies, convergent findings are beginning to materialize, and rigorous research standards are emerging. Thus, there are countless possibilities for future work. Three with particular promise are highlighted here.

Novel natural experiments

First, five natural experiments were considered in this review, but there are several others that could be used to study ovarian hormone influences on cognitive brain structures and function; some examples are depicted (by gray lines) in Figure 1 to highlight their relative hormone levels and timing during the life course. One is pregnancy, as there are huge changes in estrogens and progestagens during this relatively short time frame. There is meta-analytic evidence for cognitive deficits, especially in memory and executive functioning, in the third trimester[153], consistent with the speculation that ovarian hormones have nonlinear effects (e.g., levels that are "too high" have negative sequelae). There is also evidence from longitudinal MRI studies: women were scanned before, immediately after, and two years post pregnancy, and findings revealed increasing gray matter volume reductions in frontal and temporal regions, including the hippocampus, with effects persisting for several years[154]. This is consistent with the speculation that the brain is sensitized to organizational hormone influences during any transitional period. Other natural experiments include precocious puberty (i.e., clinically early puberty, isolating effects of age and ovarian hormones)[13], surgical menopause (with exaggerated effects compared to natural menopause)[155], hormonal intrauterine device use (which is becoming increasingly popular)[156], and gonadotropin-releasing hormone agonist treatment (that allows for precise timing of ovarian hormone cessation)[157, 158]. There are also amazing opportunities to study samples that lie at the

intersection of natural experiments, such as pubertal adolescents who initiate OC use. Such samples may be challenging to study and have limitations, but this work will undoubtedly move cognitive neuroscience forward.

Hormone interactions

Second, most work on ovarian hormone contributions to cognitive neuroscience concerns estrogens, but progestagens matter, as evidenced by provocative results from menstrual cycle, OC, and MHT research[71, 95, 143]. Future insights will likely be facilitated by new prescriptions of naturally occurring P4 versus the current study of exogenous progestins[159]. Moreover, there are suggestive interactions between estradiol and progesterone during the menstrual cycle[71] and clear indications of interactions in clinical science[152, 160] that may generalize to cognitive neuroscience. Finally, both estrogen and progestagens are neuromodulators, and have been shown to interact with neurotransmitters, including dopamine, serotonin, gamma-aminobutyric acid, glutamate, and acetylcholine[10, 17, 57, 161]. Though challenging to study in humans, the rise of spectroscopy provides intriguing possibilities for future investigations[162].

Person-specific effects

Third, most cognitive neuroscience research focuses on mean-level effects, assuming that results then apply equally to all people in a sample. Thus, there is little consideration of individual differences, and many studies attempt to statistically control for such variability (e.g., with age covariates). This could be scientifically costly. There are unmistakable individual differences in neuroendocrine processes (see Fig. 2), and other individual differences (e.g., stress, genotype, physical health, and baseline cognition) often modulate neuroendocrine links. This highlights a critical but neglected aspect of ovarian hormone

effects on cognitive brain structures and function: they are person-specific, depending upon biology, psychology, and sociocultural experiences of individual women. Person-specific effects cannot be examined in traditional between-subject analyses of inter-individual variation (e.g., standard GLMs); instead, they require within-subject analyses of intra-individual variation[163, 164]. Fortunately, fMRI data are well-suited to analyses of intra-individual variation because they provide many observations from the same individual across time (i.e., functional volumes during a scan)[165].

To demonstrate the utility of a person-specific approach to research questions about the cognitive neuroscience of ovarian hormones, illustrative fMRI data and analyses are provided from a real oral contraceptive user (using a pill with 1.5 mg norethindrone acetate and 30 μg ethinyl estradiol) scanned twice (during placebo and active phases) while completing a three-dimensional mental rotations task[166] that shows a large performance difference favoring men and typically recruits frontal and parietal regions in women[3]. Two runs (each containing 16 stimuli and 134 volumes) were acquired at each scan. After standard preprocessing and the extraction of BOLD time series from six regions of interest shown to be linked to estradiol or sex differences during mental rotations performance[166, 167], data from each scan were submitted to a sparse and data-driven person-specific network analysis approach called unified structural equation modeling (implemented within group iterative multiple model estimation)[168, 169]. Results are shown in Figure 3. It is clear that most connections present during the placebo phase (Fig. 3A) are also present in the active phase (Fig. 3B). Interestingly, however, there are more connections emanating from right hemisphere regions during the low-hormone placebo phase than the high-hormone active phase, consistent with the sex difference in right hemisphere lateralization favoring men[3]. Also, regions known to show a sex difference (e.g., right parietal)[167] or to be linked to estradiol (i.e., left superior parietal)[166] are inversely related to each other at a time lag during

the placebo phase (blue dashed line), but not during the active phase (when both were contemporaneously predicted by the left inferior frontal gyrus; red solid line). Thus, brain regions involved in sex and ovarian hormone effects appear to be modulated by exogenous hormone treatment in this individual woman. Effects, however, may differ for other, unique women, which can be uncovered in future person-specific analyses.

Conclusion

Significant progress has been made in the understanding of ovarian hormone influences on cognitive brain structures and function in the past five years, ignited in part by calls for research on sex differences and technological advances in neuroimaging and biological data analysis. Particular insight has been afforded by studies of natural experiments, such as puberty, the menstrual cycle, hormonal contraceptive use, menopause, and menopausal hormone therapy. Across studies, there is compelling evidence for estradiol effects on the structure and function (during verbal and memory tasks) of the hippocampus and PFC, emerging evidence for estradiol's interplay with dopamine during reward processing, and suggestion of complex interactions among sex hormones (including progesterone and androgen). Although inferences are limited by heterogeneity across study designs and samples, there is incredible opportunity for future research, especially concerning individual differences and biopsychosocial modulators of neuroendocrine associations in women, which has implications for advancing cognitive neuroscience to the benefit of all.

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Author Contributions

A.M.B. conceptualized the manuscript with critical input from J.S.M. Both authors drafted the manuscript and approved the final version for submission.

Competing Interests

The authors declare no competing interests.

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Figure Captions

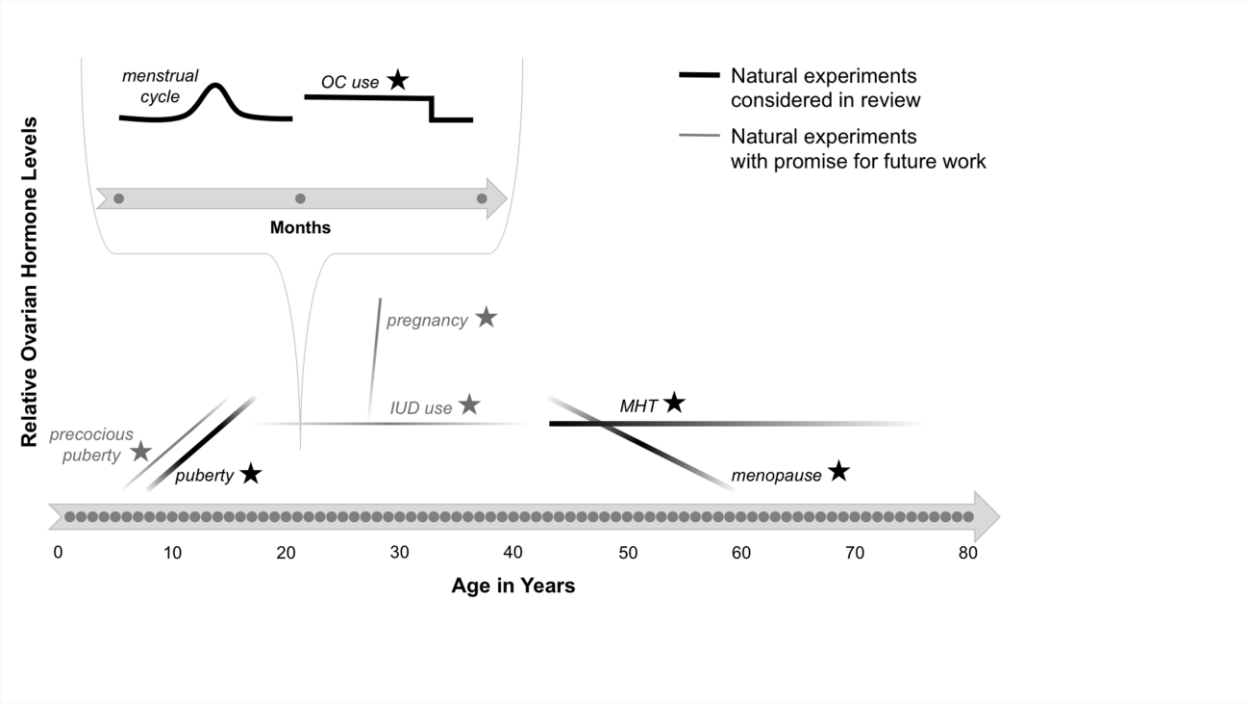


Figure 1. Depiction of natural experiments for the study of ovarian hormone influences across the lifespan. Relative levels across hormones (i.e., estrogens and progestagens) and formulations (e.g., endogenous or exogenous) are shown, as absolute levels are unknown in many cases. All natural experiments are thought to have activational effects on neurocognition, with some also having possible organizational effects (denoted with a star). Menstrual cycle and OC effects vary month-to-month (shown in inset), and the developmental timing of effects varies across individuals (denoted with fading lines). OC: oral contraceptive; IUD: intrauterine device; MHT: menopausal hormone therapy

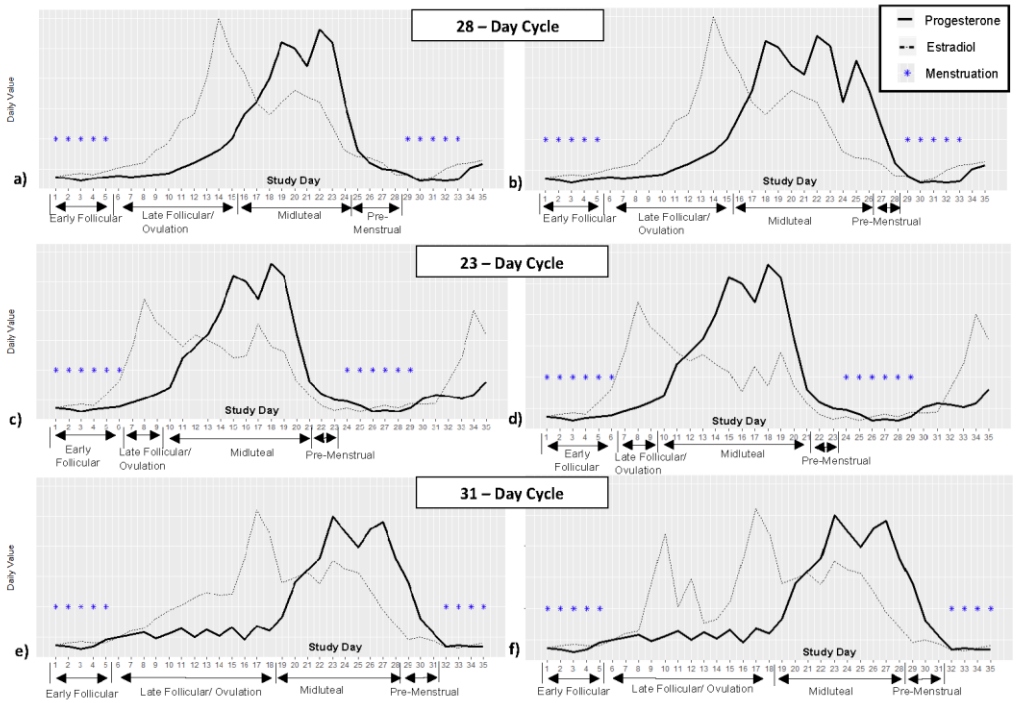
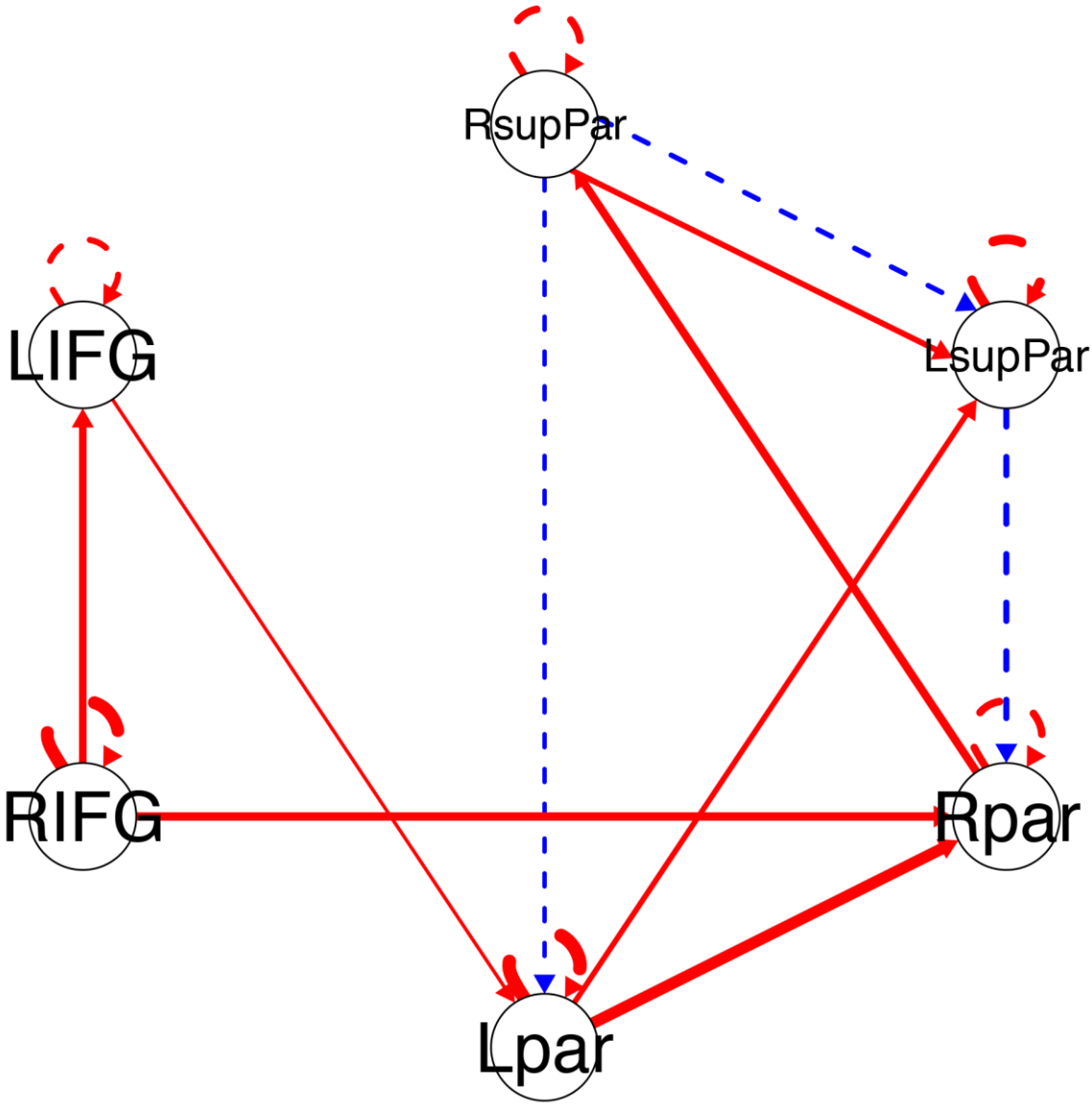


Figure 2. Examples of fluctuating estradiol and progesterone across the menstrual cycle plotted over 35 study days. Data are simulated, but empirically informed. Ovarian hormone levels vary based on cycle length and individual differences in hormonal fluctuations. This leads to inherent differences in phase timing. (A, C, E) All phases have differential timing. Although the duration of late follicular/ovulation appears to be the most prominent difference between the plots, other phases differ in length also. (B, D, F) Though not exhaustive, several ways in which ovarian hormones do not follow traditionally-established patterns. Plot B depicts a case in which progesterone presents with an additional peak following the prototypical double peak during the mid-luteal phase. Plot D depicts a case in which the second smaller peak in estradiol during mid-luteal phase is not present, showing instead several smaller peaks at lower levels. Plot F depicts a case in which estradiol spikes earlier

than expected for ovulation (typical timing is approximately 14–16 days prior to menstruation).



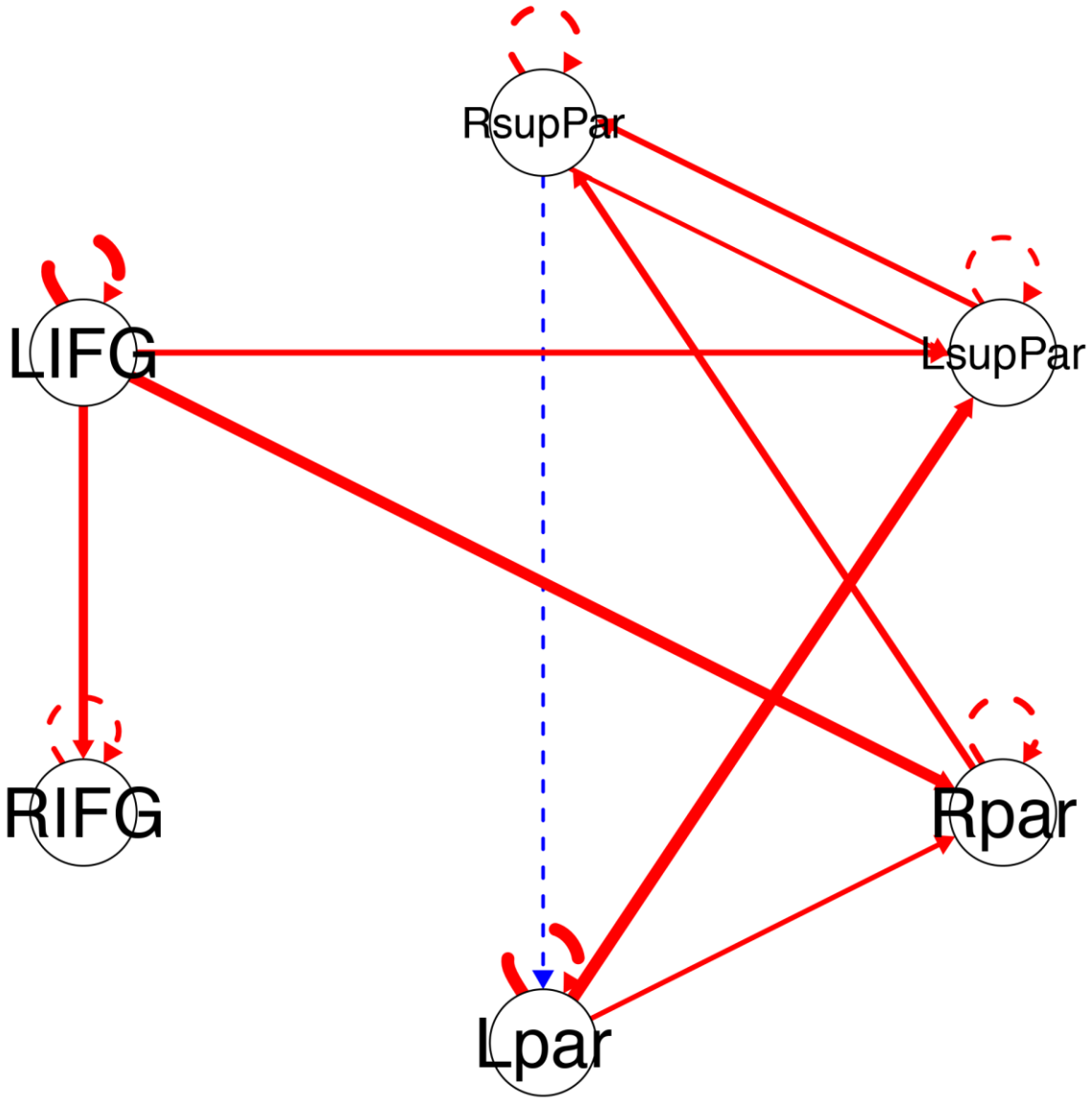


Figure 3. Person-specific network models generated from unified structural equation modeling for an oral contraceptive user (of a pill containing ethinyl estradiol and norethindrone acetate) completing a three-dimensional mental rotations task during the placebo and active pill phases; task performance was similar across phases. Functional data were collected on a GE MR750 3 Tesla scanner with a 32-channel head coil using an echo-planar imaging pulse sequence (TR = 2000 ms; TE = 25 ms; flip angle = 90˚; 64 × 64 matrix; 3 mm^3 voxels), standard preprocessing was conducted with registration to a high-resolution

T1-weighted spoiled gradient recalled acquisition structural scan (flip angle = 8°; 256 × 256 matrix; 1 mm^3 voxels), and fMRI time series were extracted from brain regions of interest (with 6.5 mm radii at Montreal Neurologic Institute central coordinates [x, y, z]: RsupPar [52, -40, 58], LsupPar [-52, -40, 58], Rpar [25, -62, 42], Lpar [-25, -62, 42], RIFG [36, 20, 22], LIFG [-36, 20, 22]) after being intersected with the structural image (to ensure no incorporation of non-brain matter). All connections among brain regions are directional, with solid lines indicating contemporaneous relations (i.e., prediction during the same volume) and dashed lines indicating lagged relations (i.e., prediction from one volume to the next). Red lines indicate positive relations, blue lines indicate negative relations, and line thickness reflects relation magnitude. Autoregressive connections (i.e., lagged connections indicating that each region predicts itself at the next volume) were estimated for all regions. (A) The network during the placebo pill phase fits the data well: $\chi^2(35) = 205.20$, $P < 0.001$, RMSEA = 0.14, SRMR = 0.04, CFI = 0.97, NNFI = 0.94. (B) The network during the active pill phase also fits the data well: $\chi^2(36) = 225.07$, $P < 0.001$, RMSEA = 0.14, SRMR = 0.04, CFI = 0.97, NNFI = 0.94. RsupPar: right superior parietal cortex; LsupPar: left superior parietal cortex; Rpar: right parietal cortex; Lpar: left parietal cortex; RIFG: right inferior parietal gyrus; LIFG: left inferior parietal gyrus. RMSEA: root mean squared error of approximation; SRMR: standardized root mean residual; CFI; comparative fit index; NNFI: non-normed fit index.

Table 1. Summary of recent cognitive neuroscience studies related to the menstrual cycle and hormonal contraceptives

Study	Participants	Type	Brain Measure	Cognitive Domain	Design	Main Findings

Arelin *et al*.[81,a]	1 naturally cycling woman, aged 32 years	Menstrual Cycle	Resting state connectivity	--	Single-subject repeated measures of endogenous hormones	- Progesterone positively correlated with greater connectivity among dlPFC, sensorimotor cortex and hippocampi
Barth *et al*.[73,a]	1 naturally cycling woman, aged 32 years	Menstrual Cycle	Hippocampal structure	--	Single-subject repeated measures of endogenous hormones	- Estradiol positivity correlated with gray matter volume and volumetric FA in hippocampus
De Bondt *et al*.[84]	18 naturally cycling women, average age 24.5 (SD = 3.9) years; 19 women using monophasic OCs, average age 23.3 (SD = 2.6) years	Menstrual Cycle & OC	Resting state connectivity, focusing on the DMN and ECN	--	Repeated measures and group comparisons	- No effects of menstrual cycle or OC use on resting state connectivity in DMN or ECN
Diekhof *et al*.[78]	15 naturally cycling women, average age 24.9 (SD =	Menstrual Cycle	Task-related function	Reinforcement learning	Repeated measures of menstrual cycle	- Greater ACC activity to negative feedback during

	1.8) years					mid-luteal versus late follicular phase, which was positively correlated with avoidance learning during mid-luteal phase - Greater avoidance learning during mid-luteal versus late follicular phase
Hjelmervik *et al*.[85]	16 naturally cycling women, average age 23.25 (SD = 5.01) years	Menstrual Cycle	Resting state connectivity, focusing on the FPN	--	Repeated measures of menstrual cycle	- No effects of menstrual cycle on resting state connectivity in FPN
Lisofsky *et al*.[70]	21 naturally cycling women (11 healthy controls; 10 PMDD patients), aged 22–31 years	Menstrual Cycle	Hippocampal structure	--	Repeated measures of menstrual cycle and endogenous hormones	- Late follicular phase showed significantly greater posterior hippocampal gray matter volume versus early follicular phase - Estradiol positively

						correlated with left parahippocampal gray matter volume
Petersen *et al*.[79]	20 naturally cycling women in early follicular phase; 25 naturally cycling women in mid-luteal phase; 22 women using OCs during placebo pill phase; 24 women using OCs during active pill phase; all aged 18–40	Menstrual Cycle & OC	Resting state connectivity, focusing on the DMN and ECN	--	Group comparisons of menstrual cycle phases and OC placebo and active pill phases	- Women in early follicular phase showed enhanced connectivity of regions within DMN versus women in the mid-luteal phase and active and placebo OC users - Women in early follicular phase showed enhanced connectivity of regions within ECN versus women in the mid-luteal phase and active OC users - Placebo OC users showed greater connectivit

						y of regions with ECN versus active OC users
Pletzer *et al*.[87]	16 naturally cycling women, average age 26.57 (SD = 6.01) years; 14 women using combined OCs, average age 23.22 (SD = 3.51) years	OC	Task-related function	Number tasks	Group comparisons	- Lower frontoparietal activations in OC users versus women in follicular phase in a number comparison task - Greater mPFC and inferior parietal lobe activations in OC users versus women in mid-luteal phase during a number comparison task
Pletzer *et al*.[95]	20 naturally cycling women in menstrual/early follicular phase, average age 26.60 (SD = 6.24) years;	OC	Regional brain structures	--	Group comparisons	- Larger bilateral fusiform, FFA, and PPA gray matter volumes in users of anti-androgenic OCs

	22 women using anti-androgenic OCs, average age 21.95 (SD = 2.85) years; 18 women using androgenic OCs, average age 24.78 (SD = 2.94) years					versus naturally cycling women - Smaller bilateral middle and superior frontal gyrus gray matter volumes in users of androgenic OCs versus naturally cycling women - No group differences in hippocampal, parahippocampal, ACC gray matter volumes
Pletzer *et al*.[82]	18 naturally cycling women, average age 26.61 (SD = 6.07) years; 16 women using androgenic OCs, average age 24.56 (SD = 3.03); 16 women using anti-androgenic	Menstrual Cycle & OC	Resting state connectivity across networks	--	Repeated measures and group comparisons	- Late follicular phase showed greater connectivity of left temporal cortex with DMN versus menstrual/ early follicular phase - Mid-luteal phase showed greater

	OCs, average age 21.56 (SD = 2.92)					connectivity of regions within DMN versus menstrual/ early follicular phase - Androgenic OC users showed increased connectivity of medial PFC with DMN versus women in menstrual/ early follicular phase - Anti-androgenic OC users showed increased connectivity of bilateral basal ganglia with FPN versus women in menstrual/ early follicular phase
Pletzer *et al*.[71]	55 naturally cycling women,	Menstrual Cycle	Hippocampal and basal	--	Repeated measures of	- Late follicular phase showed

	aged 18–35 years		ganglia structure		menstrual cycle and hormones	significantly greater hippocampal gray matter volume versus menstrual/ early follicular and mid-luteal phases, which was positively correlated with estradiol - Mid-luteal phase showed significantly greater basal ganglia gray matter volume versus late follicular/pre-ovulatory phase, which was positively correlated with progesterone
Pletzer *et al*.[75]	36 naturally cycling women, average age 25.36 (SD = 4.42) years	Menstrual Cycle	Task-related function	Spatial navigation, Verbal fluency	Repeated measures of menstrual cycle and endogenous	- Heightened hippocampal/ parahippocampal activity in pre-

					hormones	ovulatory phase during navigation and fluency - Hippocampal/ parahippocampal activity during navigation positively related to estradiol - Heightened caudate and dlPFC activity in mid-luteal phase during navigation and fluency - Caudate and dlPFC activity during navigation positively related to progesterone
Syan *et al*.[83]	25 naturally cycling women, average age 27.4 (SD = 7.7) years	Menstrual Cycle	Resting state connectivity across networks	--	Repeated measures of menstrual cycle and endogenous hormones	- No differences in network connectivity between menstrual cycle phases - Proges

						terone positively correlated with connectivity of FPN regions in late luteal phase - Progesterone negatively correlated with regions within DMN during mid-follicular phase - Progesterone positively correlated with regions within DMN during late luteal phase
Thimm *et al*.[77,b]	21 naturally cycling women, aged 18–34 years	Menstrual Cycle	Task-related function and connectivity	Cognitive control/ Attention	Repeated measures of menstrual cycle	- Greater right ACC activity during menstrual and late follicular phases versus mid-luteal phase - Greater connectivity between

						regions of FPN during menstrual versus luteal phase
Weis *et al*.[80,b]	19 naturally cycling women, aged 18–34 years	Menstrual Cycle	Resting state connectivity, focusing on the DMN	--	Repeated measures of menstrual cycle	- Greater connectivity between left middle frontal gyrus and DMN during menstrual/ early follicular versus late follicular phase

Studies since 2014 included in review. Matching superscripted letters reflect data reported from overlapping samples. ACC; anterior cingulate cortex; DMN: default mode network; ECN: executive control network; FA: fractional anisotropy; FFA: fusiform face area; FPN: fronto-parietal network; OC: oral contraceptive; PFC: prefrontal cortex; PMDD: Premenstrual dysphoric disorder; PPA: parahippocampal place area; SMA: supplementary motor area.

Table 2. Summary of recent cognitive neuroscience studies related to menopause and menopausal hormone therapy

Study	**Participants**	**Type**	**Brain Measure**	**Cognitive Domain**	**Design**	**Main Findings**
Albert *et al*.[137]	75 post-menopausal women, aged 51–74 years	MHT, short-term	Hippocampal structure	--	Repeated measures of dose-dependent estradiol treatment for 3 months	- High dose of estradiol (2 mg) showed significant increase in

						posterior hippocampal gray matter volume compared to low dose (1 mg) and placebo
Berent-Spillson *et al*.[143]	29 peri-menopausal women, aged 45–55 years	MHT, short-term	Task-related function	Verbal processing and visual working memory	Randomized, double-blind crossover of estradiol or progesterone (versus placebo) treatment	- Estradiol linked to increases in, but progesterone linked to decreases in, PFC activity during verbal processing - Progesterone linked to increases in PFC and hippocampus activation during visual working memory
Berent-Spillson *et al*.[111]	15 pre-menopausal, 11 peri-menopausal, 28 post-	Menopause	Task-related function	Cognitive control of emotion processi	Group comparisons	- During emotion processing, increasing fronto-temporal

	menopausal women, aged 42–61 years			ng		activation across menopausal transition
Berent-Spillson *et al*.[142]	38 long-term MHT users and 19 post-menopausal non-users, aged over 60 years	MHT	Task-related function	Verbal processing	Group comparisons (grouped estrogen and combined users)	- MHT users with greater frontal activation during verbal processing accompanied by some indications of worse performance
Braden *et al*.[105]	32 current users, 41 past users, and 21 non-users (all post-menopausal women), and 49 men, aged 73–91 years	MHT	Hippocampal structure	Verbal memory	Group comparisons (grouped estrogen and combined users)	- No differences between MHT users and non-users in hippocampal volume - Positive correlation between hippocampal volume and verbal memory for non-users, but

						not MHT users
Coker *et al*.[135,a]	127 estrogen, 229 combined, and 373 placebo users, all post-menopausal women aged 65 years or over	MHT	Brain structure	--	Group comparison of volumetric change from 1–3 years after treatment to 6–7 years after treatment	- No group differences in brain, ventricular, or lesion volume change - Reduced frontal lobe volumes and suggestion of reduced hippocampal volumes in MHT users versus placebo - Pattern of results did not depend on MHT formulation
Girard *et al*.[144,b]	12 early post-menopausal women, aged 48–55 years	MHT	PFC function	Cognitive control	Repeated measures of estrogen + progesterone treatment versus placebo	- Greater activity in dorsolateral PFC, ventrolateral PFC, and ACC during task switching (versus control)

						while using MHT (versus placebo), with no differences in task performance
Jacobs *et al*.[109,c]	32 pre-menopausal, 29 peri-menopausal, 31 post-menopausal women, and 94 men, aged 45–55 years	Menopause	Task-related function and connectivity	Verbal processing	Group comparisons on neural ROIs and psychophysiological interactions (with hippocampus and ventrolateral PFC seeds)	- During verbal processing, hippocampal activity decreased (correlated with declining estradiol) across menopausal transition - During verbal processing, greater hippocampal connectivity for post-menopausal compared to pre- and peri-menopausal women (correlated with declining estradiol)

Jacobs *et al*.[110,c]	26 pre-menopausal, 25 peri-menopausal, 20 post-menopausal women, and 62 men, aged 46–53 years	Menopause	Task-related function and connectivity	Verbal working memory	Group comparisons on neural ROIs and psychophysiological interactions (with dorsolateral PFC seed)	- During verbal working memory, increased dorsolateral PFC activation, but attenuated hippocampal deactivation (correlated with declining estradiol) across menopausal transition - Greater dorsolateral PFC connectivity with the hippocampus for post-menopausal compared to pre-menopausal women, which was related to verbal working memory performance for post-

						menopausal women only
Kantarci *et al*.[139,d]	29 oral estrogen + progesterone, 30 transdermal estradiol + progesterone, and 36 placebo users (all post-menopausal women), aged 42–56 years at intake	MHT	Brain structure	Global cognitive function	Randomized, double-blind trial comparing treatment and placebo groups	- Greater ventricular volume in oral estrogen users versus placebo - Suggestion of greater white matter hyperintensities in all MHT versus placebo - No differences in cognition among groups
Kantarci *et al*.[140,d]	20 oral estrogen + progesterone, 22 transdermal estradiol + progesterone, and 33 placebo users (all post-menopausal	MHT	Brain structure	Global cognitive function	3-year follow-up of randomized, double-blind trial comparing 48-month treatment of oral estrogens or transdermal estradiol with progesterone versus placebo	- Greater white matter hyperintensities in oral estrogen users versus placebo - Slower rates of dorsolateral PFC volume decline

	women), aged 42–56 years at intake					in transdermal estradiol users versus placebo - No differences in ventricular volumes or cognition among groups
Kim *et al*.[104]	20 pre-menopausal women, average age 39.9 (SD = 8.1) years, and 20 post-menopausal women, average age 55.7 (SD = 2.4) years	Menopause	Brain structure	--	Group comparisons	- Reduced gray matter volumes in supplementary motor area and other frontal and temporal regions for post- versus pre-menopausal women - Gray matter volumes in differentiated regions positively correlated with

						estradiol
Ryan *et al*.[134]	62 current users, 60 past users, 173 non-users (all post-menopausal women), and 287 men, aged 68–75 years	MHT	Brain structure	--	Group comparisons (grouped estrogen and combined users)	- Current MHT users had reduced gray matter volumes compared to past and non-users - No group differences in hippocampal, corpus callosum, or white matter lesion volume
Thomas *et al*.[145,b]	13 peri-menopausal women, aged 48–55 years	MHT	Task-related function	Reward processing	Randomized, double-blind crossover trial comparing estrogen + progesterone treatment and placebo conditions	- Greater putamen and ventromedial PFC activity during reward processing during MHT versus placebo - Estradiol during MHT positively related to putamen (and other regional)

						activity
Thurston *et al*.[113,e]	18 peri-menopausal and post-menopausal women, aged 40–60 years	Menopause	Resting state connectivity, focusing on the DMN	--	Association between DMN connectivity and hot flashes	- Positive association between physiologically-monitored hot flashes and DMN connectivity, particularly hippocampal connectivity in the DMN
Thurston *et al*.[106,e]	19 peri-menopausal and post-menopausal women, aged 40–60 years	Menopause	White matter hyperintensities	--	Association between white matter hyperintensities and hot flashes	- Positive association between physiologically-monitored hot flashes and white matter hyperintensities
Vega *et al*.[112]	31 post-menopausal women, aged 50–60 years	Menopause	Resting state connectivity, focusing on cognition-linked networks	Cognitive complaints	Association of DMN and executive function networks with cognitive complaints	- Positive association between cognitive complaints and ECN nodes,

						but not DMN nodes
Zhang *et al*.[136,a]	254 estrogen, 420 combined, and 691 placebo users, all post-menopausal women aged 65 years or over	MHT	Brain structure	--	Data driven pattern detection to identify group differences across the whole brain (1–3 years after treatment)	- Reduced frontal gray matter volume (e.g., ACC) in MHT users versus placebo, especially in estrogen only users - No white matter differences among groups

Studies since 2014 included in table. Matching superscripted letters reflect data reported from overlapping samples. ACC: anterior cingulate cortex; DMN: default mode network; ECN: executive control network; MHT: Menopausal hormone therapy; PFC: prefrontal cortex; ROI: region of interest.