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Ovarian hormones, sleep and cognition across the adult female lifespan: an integrated perspective

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Abstract

Loss of ovarian function in women is associated with sleep disturbances and cognitive decline, which suggest a key role for estrogens and/or progestins in modulating these symptoms. The effects of ovarian hormones on sleep and cognitive processes have been studied in separate research fields that seldom intersect. However, sleep has a considerable impact on cognitive function. Given the tight connections between sleep and cognition, ovarian hormones may influence selective aspects of cognition indirectly, via the modulation of sleep. In support of this hypothesis, a growing body of evidence indicates that the development of sleep disorders following menopause contributes to accelerated cognitive decline and dementia in older women. This paper draws from both the animal and human literature to present an integrated view of the effects of ovarian hormones on sleep and cognition across the adult female lifespan.

Keywords

estrogens; progesterone; menopause; hormone replacement therapy; sleep loss; memory; executive function; primate; rodent; human

Introduction

Several lines of research indicate that ovarian hormones, including estrogens (E) and progesterone (P), affect brain structure, cognition, and behavior in females across the lifespan. Most studies focus on cognitive and behavioral changes that occur following the menopausal transition, when levels of E and P gradually decline. Interestingly, this period is accompanied by sleep disruptions, hot flashes (HFs), mood changes, cognitive decline and increased risk of dementia, suggesting that the loss of circulating ovarian hormones is a key contributor to these symptoms. However, the hypothesis that ovarian hormones have a causal

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role in these symptoms has most often been examined in distinct lines of research focusing on a single domain (e.g. ovarian hormones and cognition) with little cross-talk among research fields. In this paper, we argue that a more integrated approach incorporating multiple behavioral outcomes may provide a better understanding of the effects on ovarian hormones on behavior. This review focuses on two of these domains, sleep and cognition. We first show that both sleep (reviewed in section 1) and selective cognitive abilities (reviewed in section 2) are independently sensitive to ovarian hormones in females. Further, we discuss a growing body of evidence demonstrating tight connections between sleep and several cognitive domains, including attention, executive function, and spatial memory (reviewed in section 3). Since the literature on sleep and cognition is particularly vast, we discuss specific studies on abilities shown to be sensitive to both ovarian hormones and sleep in adult females. In synthesizing these findings (Section 4), we suggest that ovarian hormones may play an important role in regulating the impact of sleep on cognitive function in females. Although limited data are currently available to support this hypothesis, as most of the studies on the interplay between sleep and cognition were conducted in mixed-sex samples where biological sex was not taken into consideration, or in male-only samples, we believe that it is an important area for future research with potential for therapeutic intervention.

1. Sleep is sensitive to ovarian hormones

1.1 Overview of sleep

Sleep is a behavior observed in most organisms, and in contrast to wakefulness, involves reduced responsiveness to external stimuli (Campbell & Tobler, 1984; Hendricks et al., 2000). Two regulatory mechanisms influence the sleep-wake cycle; biological clocks (i.e. circadian rhythms), which synchronize the timing of sleep over an ~24 hr cycle, and homeostatic drive, or the need for sleep, which increases proportionally with the time spent awake (Borbély, 1982). Changes in cortical activity that occurs during the sleep/wake cycle can be monitored using electroencephalography (EEG) and used to quantify the different vigilance states. These states include 1) *wake*, characterized by high frequency, low amplitude EEGs, 2) *rapid-eye movement* (REM), with EEGs that are similar to wake (high frequency/ low amplitude), and 3) *non-rapid eye movement* (NREM), which is further divided into three stages (N1-N3). The deepest stage, N3, is also known as *slow-wave sleep* (SWS), which involves low frequency, high amplitude EEGs (i.e. delta waves). The sleep-wake cycle typically progresses from wake, to the lightest stage of NREM (N1), then to deeper stages (N2-N3) before transitioning to REM. In adult humans, each cycle takes approximately 90 min, with a total of 3–5/night (Armitage & Hoffmann, 2001). Sleep can become disrupted by frequent awakenings (i.e. fragmented sleep), extended periods of arousals, and diminished SWS (Guilleminault et al., 1988).

1.1 Sleep quality and sleep architecture in women

Excellent reviews describing the role of ovarian hormones on sleep are available (Lord et al., 2014; Moline et al., 2004; Mong et al., 2011, 2016; Polo-Kantola, 2011), and we only briefly discuss this topic here. Sex differences have been reported in both subjective and objective sleep measures. Women are 1.3–1.8 times more likely to report sleep problems

than men (Polo-Kantola, 2011), including more disrupted and insufficient sleep (Groeger et al., 2004; Lindberg et al., 1997; Middelkoop et al., 1996; Reyner et al., 1995; Zhang & Wing, 2006), poorer sleep quality, as well as difficulty falling and staying asleep (Lindberg et al., 1997; Zhang & Wing, 2006). Although these data suggest that sleep quality is poorer in women than men, studies using objective polysomnographic (PSG) recordings do not corroborate these findings. Indeed, compared to men, women across a wide range of ages sleep for longer (Bixler et al., 2009; Ohayon, Carskadon, Guilleminault, & Vitiello, 2004; Polo-Kantola et al., 2016; Tonetti, Fabbri, & Natale, 2008; Ursin, Bjorvatn, & Holsten, 2005), have a shorter sleep onset latency, spend less time transitioning between wakefulness and sleep (Goel et al., 2005), and have more SWS and slow-wave activity (SWA; delta, ~0.5– 4 Hz) during sleep (Bixler et al., 2009; Carrier, Land, Buysse, Kupfer, & Monk, 2001; Dijk et al., 1989; Ehlers & Kupfer, 1997; Latta et al., 2005; Mourtazaev et al., 1995). In addition, the decline in SWS that occurs with age (Mander et al., 2016) has been reported to be attenuated in women compared to men (Ehlers & Kupfer, 1997; but see Carrier et al., 2001). Two other studies show that objective sleep is more resistant to sleep disruptions in young women than in young men. Vgontas et al (2004) found that changes in inflammation markers and maximum cortisol values during restricted sleep were greater in men than in women. In addition, objective sleep measures (sleep efficiency and percentage of N1) were less affected by night blood draws in women than in men in another study (Blixter et al., 2009). Overall, these findings suggest that women's objective sleep is better and more resistant to disturbances than men's. However, a few studies observe more SWA in women following sleep deprivation (SD; Armitage & Hoffmann, 2001; Manber et al., 1999), suggesting a greater accumulation of sleep debt in women than in men (Webb, 1982).

Given that many aspects of objective sleep quality appear superior in women, additional factors must contribute to the subjective experience of sleep quality. One potential factor is circadian timing, which is also influenced by sex (for a review, see Bailey & Silver, 2014). While women go to bed earlier, and wake up earlier than men (Adan & Natale, 2002; Roenneberg et al., 2007; Tonetti et al., 2008), there is some evidence that their circadian period is shorter than men's (Cain et al., 2010; Duffy et al., 2011), and that their sleep timing occurs later than their circadian timing. For instance, Cain and colleagues (2010) compared both sleep timing and circadian timing in men and women matched on age and habitual wake time. Circadian timing was estimated based on diurnal fluctuations in core body temperature and endogenous melatonin levels. The authors observed that sleep timing was equivalent across sex, but that the circadian timing was earlier in women, suggesting that sleep may be occurring at a later biological time in women. This might explain the discrepancy between subjective and objective sleep measures in women, as well as greater susceptibility to insomnia in women than in men (Zhang & Wing, 2006). However, other factors affect subjective sleep measures including depressed mood (Toffol et al., 2014), which is also more common in women (e.g., Altemus et al, 2014). Therefore, more research is necessary to fully understand why women report more sleep problems than men.

Reproductive hormones have been shown to modulate women's sleep across adulthood. Not only do sleep problems including insomnia emerge at puberty when levels of these hormones increase (Zhang & Wing, 2006), increases in sleep complaints typically coincide with periods involving large fluctuations of ovarian hormones, including puberty, pregnancy,

and the menopausal transition (as reviewed by Mong et al., 2016). There is also evidence for sleep changes across the menstrual cycle. In general, sleep appears to be poorest during the mid-to-late luteal phase, when ovarian hormones begin to decline (as reviewed by Baker & Driver, 2007; Lord et al., 2014; Moline et al., 2003). Compared to the follicular phase, the luteal phase is associated with increased reports of nighttime awakenings and arousal during sleep and decreased SWS (De Zambotti et al., 2015b). In addition, sleep spindles, which are short bursts of activity, are more frequent, longer in duration and occur in higher EEG spectral frequency (14– 17 Hz) during the luteal than the follicular phase (Baker, Kahan et al., 2007; de Zambotti et al., 2015b; Driver et al., 1996). Differences in objective sleep measures are also observed in women taking oral contraceptives as indicated by increased N2, REM, and reduced SWS relative to naturally cycling women (Baker et al., 2001a,b; Burdick, Hoffman, and Armitage, 2002). However, other studies either find limited (e.g. Romans et al., 2015) or no differences (Baker & Colrain, 2010) for sleep changes across the menstrual cycle.

The menopausal transition, which is characterized by erratic fluctuations in reproductive hormone levels followed by an eventual decline (Harlow et al, 2012) is associated with poor sleep. Forty to 60% of perimenopausal women report sleep disturbances and insomnia (Baker et al. 2015; Joffe et al., 2010; Moline et al., 2004; Polo-Kantola 2011). The menopausal transition is also associated with increased frequency of self-reported problems, such as falling and staying asleep (Kravitz et al., 2008), and reduced total sleep time (Lampio, Saaresranta, Polo, & Polo-Kantola, 2013). Levels of follicular stimulating hormone may play a role in sleep quality, as they are positively related to waking after sleep onset, number of awakenings, and arousals in perimenopausal women without sleep complaints (De Zambotti et al., 2015a). This association is independent of age, body mass index and HFs. However, studies using PSG recordings do not consistently report objectively measured sleep disruptions in menopausal women. For example, Young and colleagues (2003a) observed lower sleep satisfaction in peri- and post-menopausal women compared to pre-menopausal women, but demonstrated better sleep architecture, as indicated by better sleep efficiency (% time in bed actually asleep), more SWS, and less N2. Similarly, other studies either report better sleep patterns in postmenopausal women (e.g. Sharkey et al., 2003), or no disruptions in PSG recordings in peri- and postmenopausal women (Shaver et al., 1988). One possibility is that objectively-measured sleep disruptions during menopause are related to the occurrence of vasomotor symptoms, including HFs. Hot flashes are characterized by an intense sensation of heat, followed by sweating and skin vasodilation (De Zambotti et al., 2014; Freedman, 2014). Menopausal women with insomnia are more likely to have HFs, and the presence of HFs predicts the number of PSG-awakenings (Baker et al., 2015). De Zambotti and colleagues (2014) reported that menopausal women with insomnia exhibit an average of 3.5 HFs per night, with the majority (64%) resulting in awakenings that lasted about 16 min. The time women spent awake following a HF is negatively associated with sleep efficiency (time spent in sleep over time spent in bed), and positively associated with waking after sleep onset. These findings are consistent with previous reports (e.g. Kravitz et al., 2008), including one demonstrating an association between severe HFs and chronic insomnia in peri and postmenopausal women

(Ohayon, 2006). There is also evidence that the menopausal transition is associated with an increased risk of developing sleep-disordered breathing (Young et al., 2003b).

The most convincing evidence for a role of ovarian hormones in sleep comes from hormone therapy (HRT) studies. Postmenopausal women with HRT have a reduced latency to fall asleep (Moe et al., 2001; Schiff et al., 1979), and fewer nighttime awakenings (Erlik et al., 1981; Polo-Kantola et al., 1999; Scharf et al., 1997; Thompson & Oswald, 1977) and wakefulness (Montplaisir et al., 2001; Thompson and Oswald, 1977). E2 given for 8 weeks to peri- and postmenopausal women is associated with reduced self-reported insomnia symptoms and improved sleep quality (Ensrud et al., 2015). In addition, Moe et al (2001) reported that night blood draws result in greater sleep disruption for postmenopausal women without HRT compared to women on HRT. However, a number of studies reported no benefit of HRT on sleep (Young et al. 2003; Pickett et al., 1989; Purdie et al., 1995; Kalleinen et al., 2008). It is possible that HRT's beneficial effects on sleep are only observed in some women. For instance, HRT alleviates sleep complaints in women that experience HFs. Joffe and colleagues (2013) examined the impact of pharmacologically-induced menopause on HFs and sleep in young women (~27 years old). Administration of a gonatrotropin-releasing hormone agonist (GnRHa, leuprolide acetate) reduced levels of E2 to those observed in postmenopausal women, and resulted in HFs in 69% of participants, with the number of HFs correlating with sleep disturbances, as measured by waking after sleep onset, number of awakenings, and percent time spent in N1. Other studies also support these findings (e.g. Kravitz et al., 2008; Polo-Kantola et al., 1998a, 1999). Further, HRT might improve sleep in women experiencing depressive symptoms, as was demonstrated in a recent study (Lampio, Saaresranta, Engblom, Polo, & Polo-Kantola, 2016). This is a particularly important point, given that risk for depression is 30% to three times greater during the menopausal transition compared to the premenopausal stage (as reviewed by Maki et al., 2010), and poor sleep has been shown to be a predictor of depressive symptoms during perimenopause (Avis et al., 2001; Freeman et al., 2004; Joffe et al., 2011).

1.3 Sleep in female animals

There is considerable evidence that sex and ovarian hormones influence sleep in rodents. However, while studies in humans suggest that women sleep longer than men (Bixler et al., 2009; Ohayon et al., 2004; Tonetti et al., 2008), female rodents appear to spend less time in sleep states than males, including less NREM in mice (Ehlen et al., 2013; Franken et al., 2006; Paul et al., 2006), and REM in rats (Fang and Fishbein, 1996; Yamaoka, 1980). Rodents also demonstrate sex differences in sleep patterns, as female rodents experience higher delta power (Paul et al., 2006) than males. Several studies have shown that ovarian hormones modulate sleep behavior in female rodents and contribute to this sex difference. For example, proestrous, the phase when both E2 and P are elevated, is associated with decreased time in both REM and SWS (Hadjimarkou et al., 2008), and increased fragmented sleep (Schwierin et al., 1998) during the dark phase of the light-dark cycle. Ovariectomy abolishes both the fluctuations in sleep behavior across the estrous cycle (Mong et al., 2016), and the sex difference (Koehl, Battle, & Meerlo, 2006; Paul et al., 2006). E2 replacement in ovariectomized (OVX) rats reduces REM (Cusmano et al., 2014; Deurveilher et al., 2013; Schwartz and Mong 2011, 2013) and SWS (Deurveilher et al., 2013) during the dark phase.

Similar results are reported in mice (Koehl, Battle, & Turek, 2003; Paul et al., 2006, 2009). E2 also influences recovery from SD. When using an acute total SD procedure limited to the first 6 hr of the light phase, increased SWA and reduced sleep fragmentation was observed during the subsequent 6 hr (Schwierin et al., 1998). While recovery from SD is unaffected by estrous phase (Schwierin et al., 1998), it is enhanced by E2. Deurveilher and colleagues (2009) demonstrated enhanced REM during recovery from SD in rats that received continuous E2 replacement. A subsequent study demonstrated that continuous E2 and P replacement resulted in increased duration of REM and NREM sleep episodes, and decrease in brief awakenings during recovery sleep (i.e. during dark phase; Deurveilher, Rusak, & Semba, 2011). In middle-aged OVX rats, these hormones increase NREM-associated delta power during recovery from SD, suggesting that ovarian hormones enhance sleep intensity (Deurveilher et al., 2013). While these data suggest that E2 replacement facilitates recovery from SD, Schwartz and Mong (2013) showed that this enhancement is restricted to sleep occuring during the light phase of the light-dark cycle. In that study, estradiol benzoate (EB) replacement enhanced REM during the light phase, when rats spent most of their time asleep, but suppressed REM during the dark phase. Together, these data provide strong evidence that estrogens modulate sleep in female rats. While much of the evidence suggests that sleep is reduced by E2, the direction of the effect depends on the time of day, with E2 facilitating sleep during the light phase, when rats spend most of their time asleep, and increasing wakefulness during the dark phase when rats sleep less. Since rats are nocturnal with polyphasic sleep patterns, which differ from the consolidated sleep patterns of humans, research in diurnal animals may better model the effects of E2 on sleep in humans. We recently conducted a preliminary study (Gervais, Viechweg, et al., 2016) on the effects of E2 on sleep patterns in the common marmoset (*Callithrix jacchus*), a small primate with consolidated sleep patterns, who spends 85% of the dark phase of the light/dark cycle in sleep (Hoffmann et al., 2012). We found that E2 replacement was associated with improved sleep quality and reduced number of arousals in two middle-aged OVX marmosets, suggesting that E2 enhances sleep in this diurnal primate. These preliminary results need to be confirmed with a larger sample size, but suggest that the female marmoset is a useful model for further investigating the mechanisms by which ovarian hormones may improve sleep in women.

2. Selective aspects of cognition are sensitive to ovarian hormones

Ovarian hormones also affect cognitive function in females across the adult lifespan. Several extensive reviews are already available on this topic (Frick et al., 2015; Galea et al., 2016; Hamson, Roes, & Galea, 2016; Maki & Henderson, 2012; Maki, 2013; Sherwin & Henry, 2008). Our goal here is not to replicate this work but rather to emphasize main aspects of cognition that are both sensitive to ovarian hormones and modulated by sleep (as described in the next section). While several studies examine the impact of ovarian hormones loss on global measures of cognitive impairment (e.g. Mini Mental Status Exam), we focus on studies that examine specific cognitive abilities, as the impact of ovarian hormones on cognition is domain specific. We review findings from humans, non-human primates (NHP), and rodents implicating E2 in prefrontal cortex (PFC)-dependent cognition before switching to abilities that involve the medial temporal lobe (MTL), which includes the hippocampus

(HPC), perirhinal cortex (PRh), entorhinal cortex (EC), and parahippocampal cortex. For many abilities described below, age and reproductive stage influence the direction of results and efforts were made to review such findings separately when possible. A summary of the findings for each ability are presented in Table 1.

2.1 Attention

2.1.1 Women.—Studies in either naturally or surgically postmenopausal women report inconsistent effects of HRT on attention, with some observing no effect (Alhola et al., 2006; Gleason et al., 2015; Keenan et al., 2001; Polo-Kantola et al., 1998b; Wolf et al., 2005), while others report improved performance on at least one measure of attention in HRT users (Castonguay et al., 2015; Smith, Giordani, Lajiness-O'Neill, & Zubieta, 2001; Schmidt et al., 1996; Fedor-Feyberg, 1977). In premenopausal women, divided attention appears unaffected by menstrual phase. However, sustained attention is reduced during the luteal relative to the follicular phase, and is negatively correlated with P levels (Pletzer et al., 2014).

2.1.2 Female animals.—Inconsistent effects of hormones are also seen in animal studies. Continuous E2 replacement was found to enhance selective attention as measured by the 5-choice serial reaction time test (5-CSRTT), which requires animals to identify which of 5 locations on a screen was briefly illuminated. E2 was beneficial in young OVX rats (Bohacek and Daniel, 2010) and in older rats when given immediately, but not 5 months following OVX (Bohacek & Daniel, 2010). Another method for indexing selective attention in rats (Escobar et al., 2002), is latent inhibition (LI), which occurs when pre-exposure to a conditioned stimulus (CS) impairs subsequent learning of the CS- unconditioned stimulus (US). Latent inhibition is impaired when conditioning occurs during proestrous (Quinlan et al., 2010) or when OVX rats are treated with continuous (17–37 pg/ml) or cyclic (implant: 28 pg/ml, serum, and acute E2:10 mg/kg, s.c. every 4 days) E2 replacement (Almey et al., 2013). While these results appear paradoxical, it is possible that the latent inhibition impairment is due to enhanced Pavlovian fear conditioning rather than impaired attention to the CS during pre-exposure.

A few studies have examined the effects of ovarian hormones on attention in NHPs. While one study in young OVX monkeys found no effect of EB replacement on a Cued Search task, where they had to select a target stimulus among distractors in the presence of valid or invalid cues (Lacreuse et al., 2009), other studies using a modified Posner task, that measures the ability to shift visual spatial attention, provided consistent evidence for positive effects of HRT, in young (Voytko, 2002), middle-aged (Voytko et al., 2009) or older OVX macaques (Kohama et al., 2016). Taken together, the results from human and animal studies indicate that the effects of ovarian hormones may depend on the type of attentional process being investigated.

2.2 Executive function

Executive function encompasses a wide range of processes which require the maintenance and manipulation of working memory (WM) and which can be conceptualized as updating, task switching, response inhibition, and decision making (Chudasama & Robbins, 2006).

Given the multifaceted aspect of executive functioning, this section reviews each ability separately.

2.2.1 Updating (non-spatial) working memory

2.2.1.1 Women.: Evidence from postmenopausal women taking HRT suggests that ovarian hormones modulate non-spatial WM, so long as the task involves manipulating or updating information in WM. Estrogen replacement therapy (ERT) has no effect on simple WM tasks, like the Digit Span-forward test in postmenopausal women (Alhola et al., 2006; Castonguay et al., 2015; Duff and Hampson, 2000; Gleason et al., 2015; Keenan et al., 2001; Polo-Kantola et al., 1998b; Schmidt et al., 1996), and inconsistent findings are reported for the backward subtest, with some reporting benefits (e.g. Duff and Hampson, 2000), and others finding no effect (Castonguay et al., 2015; Gleason et al., 2015). Beneficial effects of ERT are observed on more challenging non-spatial WM tasks, including the *N*-back test & Digit Ordering tests (Castonguay et al., 2015; Duff and Hampson, 2000; Keenan et al., 2001; Krug et al., 2006). If HRT begins later in life, the benefits are not always observed. For example, on the self-ordered pointing test, one study reported no benefit of HRT in older postmenopausal women (Janowsky, Chavez, & Orwoll, 2000), while a second study reported superior performance following 2 months of ERT (Baker et al., 2012). Verbal *N*-back performance is unaffected by menstrual phase, although there is evidence for differences in patterns of activity during the task, with reduced left hemispheric activity during the late follicular phase (Joseph, Swearingen, Corbly, Curry, & Kelly, 2012).

2.2.1.2 Female animals.: Complex WM tasks used with animals typically involve functioning of both the HPC and PFC and so any impact of hormones can reflect effects on either region. The delayed recognition span test (DRST, Moss, Killiany, Lai, Rosene, & Herndon, 1997) requires monkeys to track a new stimulus in an increasing array of serially presented stimuli and can be administered in a spatial (identical stimuli, see section 2.3.1) or non-spatial form (color, object or face stimuli). In two studies using young OVX rhesus monkeys, E2 replacement was ineffective in modulating object-DRST performance (Lacreuse & Herndon, 2003; Lacreuse et al., 2009), but impaired performance on the face version (Lacreuse & Herndon, 2003), consistent with an effect of E2 on the processing of socioemotional information (e.g., Derntl et al., 2008).

In young OVX rodents, enhanced performance on non-spatial versions of the delayed spatial alternation task has been observed following continuous low E2 replacement (Wide, Hanratty, Ting, & Galea, 2004). However, impaired performance is seen following higher doses in young, middle-aged and older OVX rats (Wang, et al., 2008, 2009; Wide et al., 2004).

These studies indicate some evidence for beneficial effects of E2 on challenging non-spatial WM tasks in postmenopausal women and female rodents, but the effects depend on the E2 dose (rats), and age of subjects (women).

2.2.2. Task switching.

2.2.2.1. Women.: Task switching involves shifting attention from an initially important feature to another that subsequently conveys information about where to respond correctly to obtain a reward (Butts et al., 2013). There is accumulating evidence that ovarian hormones improve performance and/or modulate neural activation associated with the Wisconsin Card Sorting Test (WCST). A seminal study used PET to examine brain activation patterns (regional cerebral blood flow) associated with WCST performance in premenopausal women treated with a GnRHa and add-back of E or P. While no change in performance was observed, the normal dorsolateral PFC (DLPFC) activation was suppressed with GnRHa treatment and restored following E or P administration (Berman et al., 1997). Similarly, a recent study using fMRI demonstrated increased activity of the DLPFC during task switching in early postmenopausal women taking cyclic HRT. In addition, higher activity was associated with better performance (Girard et al., 2017). Another study in postmenopausal women (~60 years old), found that ERT was associated with an increased number of categories completed on the WCST (Schmidt et al., 1996) and HRT use improved performance on the number-letter task (Castonguay et al., 2015). Yet, at least one study in an elderly sample reported no benefit of 3 weeks ERT on set shifting (e.g. Duka et al., 2000).

2.2.2.2. Female animals.: E2 has beneficial effects on WCST-like performance in aged female macaques when treatment occurs soon after OVX. E2 with or without P given immediately following OVX improves performance in macaques (~20 years old; Voytko et al., 2009), but no benefit is observed 9 years after OVX (Lacreuse, Chhabra, Hall, & Herndon, 2004). Benefits are also seen on set shifting in female rats (Lipatova et al., 2016). However, E2 does not improve all aspects of task switching, as it has been shown to impair reversal learning in middle-aged marmosets (Lacreuse et al., 2014), and aged OVX rats (Gibbs et al., 2011). These studies demonstrate task-specific benefits of P or E2 on WCST and set-shifting in women and in animals, so long as treatment occurs soon after hormone loss. Overall, studies in women indicate positive effects of P or E2 on task switching, but animal studies have been sparse and inconsistent.

2.2.3 Response inhibition.

2.2.3.1 Women.: This ability can be measured by tasks that require inhibiting a prepotent response, such as the Stroop test, the Go/No-Go task or the Stop-Signal task. Improved performance on the Stroop test was observed in postmenopausal women given acute ERT (Krug et al., 2006). However, other studies do not report an effect (Alhola et al., 2006; Baker et al., 2012; Castonguay et al., 2015; Duka et al., 2000; Polo-Kantola et al., 1998b; Wolf et al., 2005). In the Go/No-Go task, subjects must produce a response for one stimulus type and inhibit responding for other stimuli, whereas in the Stop-Signal task they must inhibit responding following the appearance of a Stop signal after the response is already initiated. Impaired response inhibition was observed during the follicular phase in premenopausal women on both the Stop-Signal and Go/No-Go tasks (Colzato et al., 2010; Reimers et al., 2014), with higher E2 levels predicting poorer response inhibition (Colzato et al., 2010).

2.2.3.2 Female animals.: The effect of E2 replacement in female rodents suggests that age modulates the impact of E2 on response inhibition. Using the differential reinforcement of

low rates of responding (DRL) task, which requires withholding a response for a specified duration, Wang and colleagues (2008, 2011) reported deficits in young and middle-aged OVX rats taking E2 replacement. E2 had no effect in older rats (Wang et al., 2011). One study in baboons reported a female advantage but no effect of menstrual phase on the Stop-Signal task (Lacreuse, Gullstrand, & Fagot, 2016). Overall, there is little evidence for a benefit of HRT on response inhibition in menopausal women or older female rats. High E2 appears detrimental to response inhibition in both premenopausal women and young female rats.

2.2.4 Decision making.—There is also limited evidence that ovarian hormones modulate decision making in humans. The delayed discounting task, which assesses the ability to forego an immediate small reward for a larger delayed reward, is sensitive to the menstrual cycle: the tendency to prefer smaller immediate rewards drops from menses (low E2) to the follicular phase (high E2). The change in preference was negatively correlated with E2 levels, suggesting that higher E2 levels are associated with a decreased bias for immediate reward (Smith, Sierra, Oppler, & Boettiger, 2014). Delayed discounting performance in rats is also enhanced by higher E2 levels (Uban et al., 2012). These benefits of high E2 levels on decision making appear task specific, as no effect is seen in young or postmenopausal women on the Iowa Gambling task, in which participants must select the advantageous deck in a set of 4 decks with different pay-offs (Reavis & Overman, 2001). Additional studies are needed to draw firm conclusions about the effects of E2 on decision making.

2.3. Spatial memory

2.3.1 Spatial working memory.

2.3.1.1. Women.: There is convincing evidence that ovarian hormones are important for spatial memory, including spatial WM in many species. Although spatial WM involves both PFC and HPC function, the effects are often attributed to local effects of E2 on HPC function (Frick et al., 2015; Hamson et al., 2016). Elevated E2 levels are associated with better performance on a spatial WM task in premenopausal women (Hampson and Morley, 2013). HRT use is associated with improved spatial WM performance in one study of postmenopausal women (age: 45–65 years old; Duff & Hampson, 2000), but not in another study of older hysterectomized women (mean age 71; Schiff, Bulpitt, Wesnes, & Rajkumar, 2005).

2.3.1.2. Female animals.: Data from NHPs generally demonstrate beneficial effects of ovarian hormones on spatial WM, but point to a clear effect of age. Although young female macaques show decrements in spatial-DRST performance during the periovulatory period of the cycle (high E2; Lacreuse, Verreault, & Herndon, 2001), E2 replacement has no effect in young OVX monkeys (Lacreuse & Herndon, 2003; Lacreuse et al., 2009). Delayed Response (DR) performance is also unaffected by OVX (up to 24 month post-surgery; Voytko, 2000), and E2 replacement in young monkeys (Voytko, 2000; Hao et al., 2007). Opposing effects are observed in older macaques. One of the first observations that endocrine status modulated cognitive performance in older macaques was that peri/postmenopausal females were impaired on the DR relative to age-matched premenopausal

females (Roberts et al, 1997). Performance also correlated with estrogen metabolite levels, providing more direct support for the role of estrogens in this memory task. Later studies confirmed that HRT benefits DR (Rapp et al., 2003; Kohama et al, 2016), and spatial-DRST performance in older OVX macaques (Lacreuse et al., 2002). Conflicting results are reported in some studies, however, with either no effect of HRT in middle-aged macaques (Voytko, Higgs, & Murray, 2008), impairments following E2 replacement in OVX marmosets (Lacreuse et al., 2014) or enhanced performance in long-term OVX compared to age-matched intact females (~12 years; Lacreuse, Herndon, & Moss, 2000).

There is strong evidence for the beneficial effects of E2 on spatial WM in rodents, and unlike NHPs, this effect is independent of age. Enhanced spatial WM in young rats is observed during proestrous on the win-stay version of the radial-arm maze (RAM) task (Pompili et al., 2010). Spatial WM of young rats is also improved following E2 replacement in a number of studies using the delayed matching-to-position (DMP) task (Gibbs, 2007; Sandstrom & Williams, 2001; Velázquez-Zamora et al., 2012), the win-stay version of the RAM at a low dose (Holmes et al., 2002) or the win-shift version of the RAM following retention delays between 3–5 hr (Luine et al., 1998; but see Galea et al., 2001). In addition, Intra-cranial infusions of E2 into the medial PFC or dorsal HPC enhances win-shift performance in OVX rats (Sinopoli et al., 2006). In middle- and older-aged rats (12 & 17-month old), continuous E2 replacement given immediately, but not 5 months post OVX is associated with better performance on the win-shift version of RAM test with a 2.5 hr retention delay (Daniel et al., 2006). Other studies using cyclic administration of E2 alone, or combined with P report comparable results on the delayed spatial alternation, and D(N)MP tasks (Gibbs, 2000; Markowska & Savonenko, 2002). Thus, there is strong evidence that E2 enhances spatial WM in both humans, rodents, and older NHPs.

2.3.2 Spatial reference memory.—Spatial reference memory in rodents has most often been assessed with the fixed platform condition of the watermaze, where they have to remember the location of the hidden platform across trials. Fixed platform watermaze performance is not improved by endogenous fluctuations of ovarian hormones (Berry & McMahan, 1997; Pompili et al., 2010; Warren & Juraska, 1997), yet systemic and intra-HPC infusions of E2 following OVX enhances both the acquisition and consolidation of the task (McLaughlin, 2008; Packard & Teather, 1997a,b), so long as the treatment is given either before or immediately after acquisition. Indeed, E2 replacement reduces swimming distance in young and middle-aged rats and E2 levels correlate with performance, but E2 has no effect in old OVX rats (Talboom et al., 2008). Fixed platform acquisition is also unaffected by long-term OVX in older rats (Markowska & Savonenko, 2002).

E2 replacement also protects performance on the novel-object-in-place preference test (NOIP, aka object placement test, as reviewed by Tuscher, Fortress, Kim, & Frick, 2014), which tests rat's ability to detect a novel object and improves place learning in both young, middle-aged, and old rats (as reviewed by Korol & Pisani, 2015) by acting locally in the HPC (Zurkovsky et al., 2007). While a bias to use a spatial strategy when solving a maze is associated with proestrous in rats (Korol et al., 2004), spatial bias was associated with the late luteal phase, when P levels are high in a recent study in premenopausal women (Hussain et al., 2016).

Elevated physiological E2 levels have no effect on reference memory errors on the RAM (Fader, Johnson, & Dohanich, 1999; Holmes et al., 2002; Luine et al., 1998; Pompili et al., 2010), and long-term spatial memory (6 & 24 hr; McLaughlin et al., 2008), and but supraphysiological levels of E2 (10 μg/day) appear to increase the number of reference memory errors on the RAM (Galea et al., 2001).

2.4. Verbal memory in women

Verbal memory is also dependent on HPC function (Sherwin and Grigorova, 2011). There is a reliable female advantage in this ability (Maki, 2015), and modest effects of E2 are seen (for a review, see Maki, 2015; Sherwin, 2011). Studies examining verbal memory across the menstrual cycle provide inconsistent results (for a review, see Poromaa & Gingnell, 2014). Conflicting findings are also observed in premenopausal women who have experienced ovarian failure. For example, GnRHa given to premenopausal women resulted in verbal memory deficits in one study (Craig et al., 2008), but had no effect in others (Guerrieri et al., 2016; Owens et al., 2002). However, perimenopausal women demonstrate impaired verbal memory (Greendale et al., 2009; Weber et al., 2013), as do women that experienced surgical menopause (Sherwin, 1988). E2 replacement given to naturally (Baker et al., 2012; Castonguay et al., 2015; Jacobs et al., 1998; Kampen & Sherwin, 1994; Keenan et al., 2001; Maki, Zonderman, & Resnick, 2001; Resnick et al., 1998) and surgically menopausal women (Phillips & Sherwin, 1992b) improves verbal memory performance in some, but not all studies (e.g. Baker et al., 2012; Gleason et al., 2015; Henderson et al., 2016). Therefore, while verbal memory is affected during the menopausal transition, HRT does not have consistent effects on this ability.

2.6 Visual recognition memory

Visual recognition memory (RM) tasks assess the ability to recognize a familiar from a novel object. There is some support for a modulatory role of E2 in visual recognition memory (RM). Premenopausal women with acute ovarian suppression (via GnRHa) are impaired on the delayed matching-to-sample (DMS) task (Craig et al., 2010). In a sample of postmenopausal women, Resnick and colleagues (1998) examined the effect of ERT on regional cerebral blood flow during a visual RM test. ERT users had better RM and greater blood flow in the right parahippocampal gyrus (including the EC, PRh, and parahippocampal cortex) and inferior parietal regions, left visual association, and anterior thalamic regions. However, not all studies report benefits of HRT use on visual RM (e.g. Alhola et al., 2006; Sundermann et al., 2006). In one study, enhancements in olfactory, but not visual, RM were observed in women with AD taking ERT (Sundermann et al., 2006).

In NHPs, limited support exists for a role of E2 in RM. In younger NHPs, DMS task performance is not influenced by endogenous ovarian hormones following brief retention delays (Kromrey, Czoty, & Nader, 2015; Lacreuse et al., 2001), although a small decrement in performance is observed during the periovulatory stage following a 30-s delay (Lacreuse et al., 2001). E2 replacement in young OVX macaques also has no effect on D(N)MS task performance (Lacreuse & Herndon, 2003; Lacreuse et al., 2009), and only small beneficial effects are found in older females (Lacreuse et al., 2002; Rapp et al., 2003; Voytko et al., 2008).

A larger body of evidence supporting a role of E2 in RM comes from rodent studies. Most studies use the novel-object preference test (NOP test; also referred to as the *Novel-Object Recognition* task, the *Object Recognition Memory* task, and the *Spontaneous Object Recognition* task). Visual RM is indexed by the animals' exploration time. When rodents spend more time investigating novel than a previously-presented object, it is assumed that they recognize the familiar object. Several studies demonstrate that increased exploration of novel objects (i.e. novelty preference) following retention delays ranging from 5-min to 3 days is associated with elevated levels of E2, and that OVX eliminates this novelty preference (as reviewed by Galea et al., 2016; Luine, 2015, Tuscher et al., 2014). This beneficial effect of E2 on novelty preference is robust, and is observed in naturally cycling animals, following acute, cyclic, and continuous E2 replacement (for a review, see Galea, Frick, Hampson, Sohrabji, & Choleris, 2016; Luine, 2015; Tuscher et al., 2014), and following intra-HPC (Boulware, Heisler, & Frick, 2013; Fernandez et al., 2008; Frick et al., 2015; Lewis, Kerr, Orr, & Frick, 2008; Phan et al., 2012; Tuscher et al., 2016) and intra-PRh (Gervais et al., 2013, Gervais, Hamel et al., 2016) infusions of E2. However, novelty preference and DNMS tasks may measure different aspects of RM. In the same group of rats that demonstrated enhanced novelty preference following cyclic and intra-PRh infusion of E2 (Gervais et al., 2013, Gervais, Hamel et al., 2016), reduced accuracy on the DNMS task was observed. The vehicle-treated animals in these studies failed to demonstrate novelty preference, yet performed better on the DNMS task, indicating that rats can have intact RM and still fail to demonstrate a preference for the novel object. Thus, findings from NOP tasks should be interpreted with caution. Taken together, these studies indicate that the beneficial effects of E2 on visual RM are small or inexistent in primates, but consistently positive in rodents, unless when acting locally in the PRh.

2.6 Summary

Spatial memory and strategy are shown to be sensitive to E2 across species. However, these effects depend on task parameters (Korol & Pisani, 2015), dose (Galea et al., 2016; Hamson et al., 2016; Sherwin, 2011), age (Galea et al., 2016; Hao et al., 2007, Lacreuse, 2006), and the timing of treatment initiation (Galea et al., 2016; Hamson et al., 2016; Maki, 2013; Sherwin & Henry, 2008. Studies in rats demonstrate that this enhancement is likely due to local effects of E2 on the dorsal HPC. However, the PFC also contributes to spatial WM, and so the beneficial effects of E2 can result in local effects in either region. In addition to the strong evidence for the benefits of E2 on spatial WM, reference memory and spatial strategy, studies also show important morphological and physiological effects on the HPC that can promote these abilities, including increased volume (Lord et al., 2008), synaptogenesis, neurogenesis, protection after brain injury, and increased excitatory neurotransmission (as reviewed by Galea et al., 2016; Frick et al., 2015; McEwen & Milner, 2017).

There is also evidence that ovarian hormones modulate certain abilities dependent on the PFC, including complex nonspatial WM, and task switching (but not reversal learning). However, age, timing and type of hormone regimen, and task demands influence whether benefits are observed. While there are inconsistent findings regarding the impact on attention, it may be due to task parameters. Ovarian hormones do not appear to influence simple WM tasks, and only a limited number of studies have examined decision making. It

is currently unclear why these hormones might impact some of these abilities and not others, so additional studies, particularly in animals, are needed to clarify these differences. Emerging evidence shows the beneficial effects of E2 on the mPFC of rodents (as reviewed by Frick et al., 2015; Frankfurt & Luine, 2015), and PFC in NHPs (Bailey et al., 2011; Hara et al., 2015; Hao et al., 2006, 2007; Wang et al., 2013), consistent with the idea that E2 may influence some of these ability through direct effects on the PFC. E2 is also an important modulator of neurotransmitters such as dopamine, acetylcholine, serotonin, glutamate and GABA, all of which can influence PFC-dependent cognition. For instance, E2 has enhancing or impairing effects on non-spatial WM depending on dopamine levels (Jacobs and D'Esposito, 2011), and dopaminergic drugs can influence the effect of E2 on LI (Almey et al., 2013). Clearly, more attention is needed to understand the discrepant results reported in the literature.

A small number of studies show that the PRh is also impacted by E2 (Fonseca et al., 2013; Gervais et al., 2015). This structure, which is important for visual RM (Brown and Aggleton, 2001), is emerging as an important early marker for AD, as neurofibrillary tangles develop in the PRh before moving onto the HPC (Braak & Braak, 1991), and atrophy has been shown to occur in preclinical AD (Wolk et al., 2017). Thus, additional focus is needed on extrahippocampal structures and the abilities that depend on them, particularly in the context of understanding E2's role in cognitive aging.

Next, we present evidence that the cognitive abilities that are modulated by ovarian hormones are also impacted by sleep. Unfortunately, most of these studies were conducted in either mixed-sex samples where biological sex was not factored in, or in the case of animal studies, male-only samples. Therefore, it is currently unknown whether the impact of sleep on cognitive function might be sex-specific. A summary of findings is presented in Table 2.

3. Impact of sleep on cognitive functioning

The relation between sleep and cognition has been extensively studied in humans, as described in several excellent reviews (Alhola & Polo-Kantola, 2007; Killgore, 2010; Walker, 2008; Walker, 2009). The impact of chronic sleep loss on neural, and glial function in the CNS, which is described elsewhere (Zhao et al., 2017), provides potential mechanisms through which sleep may impact cognition. Sleep disturbances produce deficits in a wide range of cognitive domains including attention, executive function, and memory. This section provides a brief review of the literature on the impact of sleep on these specific cognitive domains, as they have also been shown to be sensitive to ovarian hormones. The goal of this section is to link the evidence that sleep impacts the same abilities that are enhanced by ovarian hormones. This will provide a basis for the next section, which discusses the few studies that have addressed whether ovarian hormones may impact cognition in part via effects on sleep.

First, we review data demonstrating the impact of SD on abilities that depend on the PFC (including WM, attention, and executive function). Unless otherwise stated, SD procedures below will involve acute total SD, which is the most common experimental model of sleep

loss (Alhola and Polo-Kantola, 2007). In the second section, we cover the importance of sleep in memory consolidation of abilities that dependent on structures of the MTL. Whenever possible, we characterize the associated neural substrates, emphasize aging effects and incorporate studies in animal models (reviewed in McCoy & Strecker, 2011). It is important to note that animal studies examining the relationships between sleep and cognition are still very sparse, and particularly lacking in NHPs. The mechanisms by which sleep affects cognition have been reviewed in detail elsewhere (Abel et al., 2013; Tononi and Cerelli, 2014) and will not be emphasized here. One influential theory, the synaptic homeostasis hypothesis, proposes that the fundamental function of sleep is the restoration of synaptic and cellular homeostasis, by which the costly synaptic strengthening that is required during wake is normalized during sleep (Tononi and Cirelli, 2014). Synaptic renormalization during sleep, largely through SWA, could explain many of the benefits of sleep on learning and memory.

3.1 Sleep and Attention

Attention regulation is a key function of sleep. It is well known than one effect of SD is the inability to pay attention effectively the following day. Multiple aspects of attention are affected, including vigilant (sustained) attention, reaction time, divided attention and selective attention, but the effects on sustained attention, which are the most robust and reliable, are thought to account for most of the deficits.

In the psychomotor vigilance test (PVT), a classic test to measure vigilant attention, SD results in an overall slowing of responses, increases of errors of commission and long lapses, as well as unpredictable behavior (as reviewed by Lim and Dinges, 2008). Even one night of partial sleep restriction (PSR) results in slower responses on the PVT (Rossa et al., 2014). Interestingly, male rats exposed to 24h of SD (Christie et al., 2008), or 28 hr of PSR (Deurveilher, Bush, Rusak, Eskes, & Semba, 2015) show strikingly similar results. However, attention appears to recover following longer PSR (52–148 hr; Deurveilher et al., 2015). The attentional performance of rats is also impaired on the 5-CSRTT, as shown by longer response latencies and increased number of errors and omissions after 4, 7, and 10 h of SD (Córdova et al., 2006).

Studies on divided attention, the ability to perform concurrent tasks, or on selective attention, the ability to focus cognitive on particular targets (locations, objects, or features) while ignoring irrelevant distracters, have produced more mixed results. Lim and Dinges' (2010) meta-analysis of 70 studies revealed that short term (< 48h) SD causes deficits in a wide range of cognitive tasks, but that most deficits can be attributed to impairments in sustained attention. Not unexpectedly, neuroimaging studies focusing on brain activation after acute SD show decreased brain activation in the fronto-parietal attention network (PFC and intraparietal sulcus) and in the salience network (insula and medial frontal cortex), as well as increased thalamic activation (meta-analysis of 11 neuroimaging studies Ma, Dinges, Basner, & Rao, 2015). With regard to aging, consistent reports indicate that the effects of SD on attentional tasks are actually greater in young adults than older adults (Adam et al., 2006; Duffy et al., 2009; Sagaspe et al., 2012) perhaps due to the effective recruitment of compensatory mechanisms in the aged brain (Sagaspe et al., 2012).

3.2 Sleep and Executive Function

It remains unclear whether tasks that require higher level cognitive capacities, such as tasks of executive function are specifically affected by sleep disturbances or whether the deficits can be explained by deficits in attentional resources.

3.2.1 Non-spatial working memory (WM).—Both accuracy and response times are significantly affected by SD in several WM tasks (Lim and Dinges, 2010). However, there is evidence that the non-executive aspects of the tasks, such as simple reaction time, can account for most of the deficits (Tucker et al., 2010, 2011).

3.2.3 Task switching.—Some studies report profound deficits on tasks requiring mental flexibility and attention shifts, such as the WCST in patients with sleep disorders (as reviewed by Fulda and Schulz, 2003). While one night of SD does not affect WCST in a healthy population (Binks et al., 1999), 5 nights of PSR do (Herscovitch et al., 1980), suggesting that a minimum amount of sleep loss is necessary to detect effects on task switching. Other studies find that sleep-deprived individuals showed greater switch costs, indicating that sleep loss reduces the capacity to modify behavior rapidly and flexibly to changing demands (Heuer et al., 2004; Jennings et al., 2003). Task switching in rats, as measured by the attentional set shifting task, is also sensitive to sleep loss (i.e. 3 and 24 hr of sleep fragmentation; McCoy et al., 2007).

3.2.4 Response inhibition.—Drummond and colleagues (2006) reported impaired ability to withhold a prepotent response (No-Go stimuli) on a Go/No-Go task following 23, 32 and 55 hr of SD. Interestingly, only the 55 hr test session also impaired the ability to respond correctly to “Go” stimuli, suggesting that inhibitory control was specifically impaired despite relatively intact attention. In a mixed-sex sample, 4 nights of PSR (6 hr/night) negatively impacted the rate of false alarms on the Go/No-Go task (Demos et al., 2016). The impact of sleep loss on response inhibition has been shown in both young and older people (Sagaspe et al, 2012). A cumulative effect of several nights of PSR may be necessary to detect an effect, as one night of PSR did not alter performance on an emotional version of the Go/No-Go task (Rossa et al., 2014).

Response inhibition is also disrupted by sleep loss in rats. Kamphuis and colleagues (2016) showed that PSR (4 hr sleep/day) for 7 days resulted in decreased behavioral control and increased bursts of responses on the DRL task. The importance of sleep on response inhibition in rats is also observed using the Go/No-go task (Borquez et al., 2014).

3.2.5 Decision making.—The impact of SD on decision making is described in detail in a recent review. For example, Killgore and colleagues (2006) used the Iowa gambling task to compare patterns of decision making at baseline and following 49 hr of SD. Under normal conditions, subjects learned to avoid large payoff high-risk decks in favor of decks providing modest but more consistent payoffs. After two nights of sleep loss, however, these same subjects tended to prefer riskier selections, despite the long-term losses that resulted. This same pattern was replicated in a second study with SD extended to 75 hr (Killgore et al., 2007). Interestingly, administration of caffeine did not reverse the deficit, suggesting that the

impairments were not simply due to deficits in alertness and sustained attention. Performance during a gambling task was also influenced by SD in a young mixed-sex sample (Fraser, Conduit, & Phillips, 2013), with participants failing to reduce their bets when risk increased and time to respond decreased. Other studies also show detrimental effects of sleep loss on decision making and risk taking (e.g. Killgore, Kamimori, & Balkin, 2011; Lei et al., 2016; Rossa et al., 2014), although some studies fail to find a difference (for a review, see Womack et al., 2013, Harrison & Horne, 2000). For example, 4 nights of PSR had no effect on performance on the Balloon Analogue Risk Task (Demos et al., 2016). Others argue for dissociable effects on different decision-making tasks (e.g. Womack et al., 2013), including Libedinsky and colleagues (2013), who observed impairments on effort discounting, but not delay discounting in the same subjects.

3.3 Sleep and Medial Temporal Lobe-dependent Memory

Sleep impacts all aspects of long-term memory (Mander et al., 2016), including acquisition, consolidation, and retrieval. In humans, SWS is important for the consolidation of declarative memories (Peigneux, et al., 2001; Rauchs, Desgranges, Foret, & Eustache, 2005; Smith, 2001), which involves the HPC and other structures of the MTL (Preston and Eichenbaum, 2013). The consolidation process allows for initially unstable memories to be integrated into a network of more stable memory representations.

3.3.1 Spatial Memory—Numerous studies indicate an important role of SWS in spatial memory consolidation. HPC neurons that are active while rodents explore a novel environment are called place cells (O'Keefe and Nadel, 1978). Wilson and McNaughton (1994) recorded the activity of place cells in rats during acquisition of a spatial task, and again during subsequent sleep. The same cells that fired together during encoding tended to fire together during subsequent SWS, and cells that did not fire during training tended to not fire during SWS. This pattern of activity is consistent with the idea that HPC activity during SWS may be involved in spatial memory consolidation. Using cerebral blood flow measurements, Peigneux and colleagues (2004) demonstrated similar results in humans, in that hippocampal areas that were activated during a virtual route learning task were re-activated during subsequent SWS. They also showed that this re-activation during SWS correlated positively with the degree of improvement on the retention test. A subsequent study provides further support for a role of HPC activity during SWS in spatial memory consolidation. Rasch and colleagues (2007) trained participants on a spatial (HPC-dependent) and a finger sequence tapping (HPC-independent) task during simultaneous presentation of an odor cue as a contextual stimulus. Participants then slept in a MRI scanner, and functional images and sleep parameters were taken. The contextual odor or a control odor were presented during SWS or REM. Significant HPC activation was revealed during SWS when the contextual odor was presented. There was no effect during REM, nor during presentation of the control odor. Re-presentation of the contextual odor during SWS led to enhanced performance on the spatial memory, but had no effect on the finger tapping task. Together, these studies support the role of SWS in spatial memory consolidation.

Very few studies have examined the relationships between sleep and spatial memory in NHPs, but they support a beneficial effect of sleep in spatial performance. For example,

Haley and colleagues (2009) reported a negative association between sleep latency/wake bouts and performance on a spatial navigational task in older female macaques. Similar results were obtained by Rahman and colleagues (2013) in a study examining the impact of SD on spatial memory in mouse lemurs. They trained male mouse lemurs on a modified version of the Barnes maze, and tested them 24 hr later. Subjects received 8 hr of SD either before training, or immediately before testing. Only those that received SD immediately before testing demonstrated impaired performance. However, SD following learning may also disrupt spatial memory consolidation. Smith and colleagues (1998) selectively disrupted REM sleep in male rats following training on the win-stay version of the RAM. Rats received 4 hr of SD either immediately, 4 hr, or 8 hr after training. Only those that received SD immediately following training demonstrated impaired performance, although the deficits were restricted to reference memory errors. Spatial reference memory impairments are also observed following sleep loss in other studies (e.g. Ward et al., 2009), while spatial WM deficits can be seen following 5–7 days of intermittent hypoxia (Row et al., 2007). NOIP performance of male rodents is impacted by SD occurring soon after encoding in some (e.g. Inostroza et al., 2013; Ishikawa et al., 2014), but not all studies (i.e. Palchykova et al., 2006). Taken together, these studies demonstrate that sleep is important for spatial memory, with some evidence suggesting that reference memory may be more sensitive to sleep loss than working memory.

3.3.2 Verbal memory—Studies have addressed the impact of sleep on verbal memory. For example, Drummond and colleagues (2000) showed that 35 hr of SD impaired free recall, but not recognition relative to a rested state. While these results suggest that sleep loss negatively impacts recall, Lutsey and colleagues (2016) reported no association between objective sleep parameters (sleep fragmentation and sleep duration) on changes in performance on recall in individuals with obstructive sleep apnea. Positive effects of sleep was reported in two studies, where sleep immediately after verbal learning of word pairs protected memory from interference (Sheth and colleagues 2012; Ellenbogen et al., 2009). In addition, Maki and colleagues (2008) found that sleep duration and objective measures of HFs predicted performance on the delayed logical memory test, but not the California Verbal Learning Test, in midlife women. Another study demonstrated that SWS and not REM influenced word recognition judgements. A mixed-sex sample was presented with a word list prior to sleep dominated by either SWS, which occurs during early sleep or REM, which occurs during late stages of sleep. PSG recordings were measured and confirmed differences in SWS and REM during the early and late sleep phases. The authors demonstrated that SWS-dominated early sleep improved recollection-based judgements (recognition with episodic memory), but had no effect on familiarity-based judgements (recognition without episodic memory; Daurat et al., 2007). Similar effects were reported by Drosopoulos and colleagues (2005). One important limitation to the procedures used in these studies is that the time of day varied between the learning and test phases for the early and late sleep conditions. Nesca and Koulak (1994) demonstrated that sleep immediately following learning improved word recognition compared to delayed sleep. However, when the learning and testing phases were matched by time of day, no differences emerged, suggesting that the effect of sleep on performance may result from effects of circadian timing.

3.3.3 Visual recognition Memory—There are limited studies examining the impact of sleep on object RM. While 4 hr of SD is insufficient to impact object recognition memory in male mice (Ishikawa et al., 2014), 6 hr immediately following object exploration does prevent novelty preference (Palchykova et al., 2006). Studies in humans (mixed-sex) also provides support for the idea that sleep impacts visual RM (e.g. Acheson et al., 2007; Mograss et al., 2009). Additional studies, particularly in NHPs are needed to further investigate potential effects of sleep on visual RM.

3.4 Summary

SD has detrimental effects on abilities dependent on the PFC, including sustained attention, task switching, and response inhibition. Decision-making is impaired by short-term SD, but there is some suggestion that it can recover following chronic PSR. While deficits are also observed on non-spatial WM tasks, they likely result from reduced sustained attention.

Memory abilities dependent on structures in the MTL are influenced by sleep. SWS appears to be particularly important for spatial memory consolidation. Too few studies have been conducted on verbal memory and visual RM to draw any firm conclusions.

A few limitations from these studies are worth noting. In most cases, an acute total SD procedure was used, when chronic PSR and chronic sleep fragmentation are more representative of sleep problems experienced by individuals with sleep complaints/disorders. Chronic PSR is common, affecting approximately 30% of adults in the US (Olds et al., 2010). As such, it is crucial to correctly model these sleep patterns to strengthen our understanding of the impact sleep on these abilities. A second limitation is the paucity of animal studies, especially in NHPs. Such studies are needed to clarify the effects of sleep on specific cognitive abilities and identify the underlying mechanisms. A third limitation concerns the lack of attention paid to the biological sex of the participants. Among the studies reviewed above, most animal studies used exclusively males. In human studies, only a handful reported the biological sex of participants and even when they did, the effect of sex was not analyzed. As described by Hamson and colleagues (2016), there are sex differences in many cognitive abilities, with a male advantage emerging for many spatial abilities and a female advantage for many verbal abilities. These sex differences can obscure the effects of sleep on these abilities, making the omission of sex as a biological variable a major problem of these studies.

4. Ovarian hormones, sleep and cognition in females

Sleep disturbances may have a differential impact on cognitive function in men and women, due in part to the influence of sex hormones. However, very few studies to date have addressed this issue. The few reports available point to a sex difference in the impact of sleep on cognition. Genzel and colleagues (2012) provide evidence that sleep may enhance HPC-dependent memory in men, but not in women. They tested a young mixed-sex sample on a paired-associates test following a nap and compared performance to a group that did not take a nap. The women in the sample were in the menses phase of their cycle. Improved memory performance, and increased spindle activity during the nap was observed in men, but not women (Genzel et al., 2012). Studies using SD suggest that selective aspects of

cognition are more sensitive to sleep disturbances in young men than women. In one study (Binks et al., 1999), estimated IQ (as measured by a short-form of Wechsler Adult Intelligence Scale-Revised) following 35 hr of SD was better in young women than men following SD, despite men scoring higher than women in the non-SD condition. However, sex differences were not observed for any other ability assessed, including sustained attention, word fluency, and cognitive flexibility. Another study reported poorer sustained attention (as indicated by slower response times) in young men than women following 38 hr of SD (Corsi-Cabrera et al., 2003). To our knowledge, the role of sex hormones in these sex differences has not been objectively investigated. However, the results are consistent with a protective role of ovarian hormones against SD induced-cognitive dysfunction in adult women.

Consequently, the loss of ovarian hormones following menopause could have a greater impact on sleep and thereby cognition in women than in men. Unfortunately, very few data are available to test the validity of this hypothesis. In a recent study in participants over 65, Chiu, and colleagues (2016) reported greater impairment in global functioning (as measured by the Mini Mental Status Exam) in women than men but the impact of sleep on cognition was not greatly affected by biological sex. Among men that had cognitive impairment, snoring, difficulty breathing during sleep, and prolonged sleep were related to scores on the Mini Mental Status Exam, whereas in women, only prolonged sleep was associated with cognitive scores. Additional studies are needed to determine whether the relationships between sleep and cognition differ between men and women and whether they change with age.

Findings from studies examining the effects of ovarian hormones on sleep and cognition in women have been inconsistent. Alhola and colleagues (2005) compared postmenopausal (58–72 years old) HRT users to non-users on attention, visual episodic memory, and visuomotor performance. Rebound sleep following SD enhanced performance on all abilities, however HRT use did not impact the effect of sleep on performance. Similarly, HRT use in postmenopausal women (59–72 years old) did not influence sustained attention following a longer 40 hr of SD (Karakorpi et al., 2006). In contrast, a study by Saletu (2003) reported that HRT (E valerate alone or in combination with a progestin) for two months improved subjective and objective sleep quality (trend) as well as sustained attention and processing speed in postmenopausal women. Cognitive processing capacity and perceptual processing resources were also improved by the combination therapy. The studies reporting negative results used small sample sizes and focused on a limited set of cognitive domains. While sleep is important for sustained attention, which was assessed in these studies, other abilities including response inhibition, task switching, decision making, and spatial memory are also sensitive to sleep. Further research is needed to address whether ovarian hormones regulate the impact of sleep on these abilities.

There is a paucity of animal studies focusing on the relations between ovarian hormones, sleep and cognition. A recent study in female rats suggests that ovarian hormones do regulate the effect of SD on MTL-dependent cognition, as assessed by performance on the fixed-platform watermaze task. Subjects included female rats that were OVX or gonadally intact. One set of subjects received 72 hr of SD, whereas the rest slept normally. SD

impaired performance, but only in the OVX animals (Esmaeilpour et al., 2015). These results suggest that circulating levels of ovarian hormones may protect against the detrimental effects of SD on spatial memory consolidation. Despite these interesting results, no other study to our knowledge has addressed the impact of ovarian hormone loss on the association between sleep and memory in animals.

If ovarian hormones benefit sleep and protect the young female brain against the detrimental effects of sleep disturbances on cognition, the loss of ovarian hormones at menopause would be expected to have adverse consequences, first by increasing sleep disturbances and second by potentiating their impact on cognitive function. As reviewed in section 2, increased sleep disturbances are observed at menopause. In addition, accumulating evidence suggests that sleep dysfunction may accelerate age-related cognitive decline and potentially conversion to AD (Mander et al, 2016; Musiek & Holtzman, 2016).

Sleep dysfunction, characterized by reduced SWS quality, duration and increased sleep fragmentation, becomes more prevalent with advancing age (Ohayon et al, 2004). However, there are large individual differences in the type and severity of age-related sleep deterioration (Vitiello, 2009), which suggest the existence of underlying pathology such as AD in certain individuals (Mander et al, 2016). People with mild cognitive impairment or AD have much more severe sleep impairments than cognitively normal older adults (Hita-Yanez et al, 2012; Prinz et al, 1982, Westerberg et al, 2012). Importantly, sleep dysfunction may occur in the very early stages of AD, often before the appearance of any other symptoms (Mander et al, 2016; Lim et al, 2013) and the magnitude of sleep disruption correlates with disease severity. Cerebrospinal fluid (CSF) Tau and β-amyloid (Aβ) protein levels can predict the degree of decreased SWS, sleep efficiency and REM sleep in AD patients (Liguori et al, 2012). In addition, CSF orexin levels, which promote wakefulness, are associated with sleep deterioration, Tau levels, and cognitive decline in AD patients (Liguori et al, 2014). This and parallel evidence from murine models of AD (e.g., Kang et al, 2009, Roh et al, 2014) have led to the hypothesis that sleep dysfunction may have a causal role in the pathophysiology of AD (Mander, 2016; Musiek and Holtzman, 2016). Importantly, recent data indicate that SWS sleep increases the rate of Aβ clearance by twofold in the mouse brain, suggesting one mechanism by which sleep may benefit brain function (Xie et al, 2013).

Postmenopausal women are at greater risk for AD than men of the same age, and sex differences in longevity only partially explain this higher risk (Snyder et al., 2016). Further, surgical removal of the ovaries prior to natural menopause increases the risk of dementia (as reviewed by Au et al., 2016). Ovarian hormone loss during the menopausal transition has been hypothesized to contribute to the increased risk for AD (Janicki and Schupf, 2010). The data reviewed in sections 2, 3 and 4, suggest that sleep may be a key component linking estrogen loss to dementia risk. Whether the loss of ovarian hormones during menopause increases the risk of dementia in vulnerable women by specifically disrupting sleep certainly warrants experimental investigation. A proposed model illustrating potential pathways through which ovarian hormone loss may contribute to specific cognitive impairments and dementia is presented in Figure 1.

Conclusion

Strong support exists for a modulatory role of ovarian hormones on sleep across species. Sleep problems in women emerge during puberty and fluctuate across the menstrual cycle. The menopausal transition is associated with decreased sleep quality and among those that also experience HFs or depressive symptoms, more PSG-awakenings. HRT improves sleep in some, but not all studies. More robust evidence comes from animal studies, where E2 modulates both spontaneous sleep, and recovery from SD.

Ovarian hormones also modulate certain cognitive abilities in adult females, and the direction of effects is influenced by several factors including age, duration of hormone loss, hormone regimen (acute, continuous, cyclic), and task demands (Galea et al., 2016; Hamson et al., 2016; Korol & Pisani, 2015). Generally, elevated levels of ovarian hormones are beneficial for sustained attention, manipulation of WM, task switching, and spatial, verbal, and recognition memory. Local effects of E2 in certain brain regions may also influence whether performance is enhanced or impaired.

Numerous studies demonstrate that sleep impacts cognition, including sustained attention, task switching, response inhibition, decision making, and memory. Most of these studies include male-only samples or mixed-sex samples where biological sex was not considered as a variable. The few studies that have examined sex differences suggest that sleep has a greater impact on cognition in young men than in young women. These as well as rodent data suggest that circulating ovarian hormones may protect the female brain from the detrimental effects of sleep disruptions.

Such a relationship would have important implications for age-related cognitive decline and dementia in postmenopausal women. Indeed, sleep disturbances increase during the menopausal transition. In vulnerable women, sleep disruptions may exacerbate cognitive decline, increase inflammation and synaptic damage and eventually set in motion a cascade of events leading to neurodegeneration (Mander et al, 2016; Musiek and Holzman, 2016). Although it is now well established that HRT does not improve cognitive symptoms in women with AD (Henderson, 2014), it is still unclear whether HRT given decades before the disease onset may provide cognitive benefits later in life (Henderson, 2014). Importantly, the onset of sleep dysfunction may precede AD symptomology and pathology by several years. Sleep may therefore provide a new target for therapeutic intervention. The development of appropriate animal models will be crucial to determine whether interventions that restore sleep patterns may protect the female brain from neurodegeneration later in life and whether HRT may provide therapeutic benefits.

List of abbreviations

5-CSRTT	5-choice serial reaction time test
Aβ	β-amyloid
AD	Alzheimer’s Disease
DMP	delayed matching-to-position

DNMP	delayed nonmatching-to-position
DMS	delayed matching-to-sample
DNMS	delayed nonmatching-to-sample
DR	delayed response
DRL	differential low rates of responding task
DRST	delayed recognition span test
E	estrogens
E2	17β-estradiol
EB	estradiol benzoate
EC	entorhinal cortex
EEG	electroencephalography
ERT	estrogen replacement therapy
FSH	Follicular stimulating hormone
GnRHa	gonadotropin-releasing hormone agonist
HFs	hot flashes
HPC	hippocampus
HRT	hormone replacement therapy
MTL	medial temporal lobe
N1-N3	stages 1–3 non-rapid eye movement
NHP	non-human primate
NOIP	novel object-in-place preference
NOP	novel-object preference
NREM	non-rapid eye movement
OVX	ovariectomized
P	progesterone
PFC	prefrontal cortex
PRh	perirhinal cortex
PSG	polysomnogram
PSR	Partial sleep restriction

PVT	Psychomotor vigilance test
RAM	radial-arm maze
REM	rapid eye movement
RM	recognition memory
SD	sleep deprivation
SWA	slow-wave activity
SWS	slow-wave sleep
WCST	Wisconsin card sorting test
WM	working memory

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Highlights

- Sleep is modulated by ovarian hormones in females across adult lifespan
- Ovarian hormones also influence certain cognitive domains
- Sleep loss impacts similar abilities, but biological sex often not considered
- Animal models are crucial for understanding the benefits of sleep on cognition

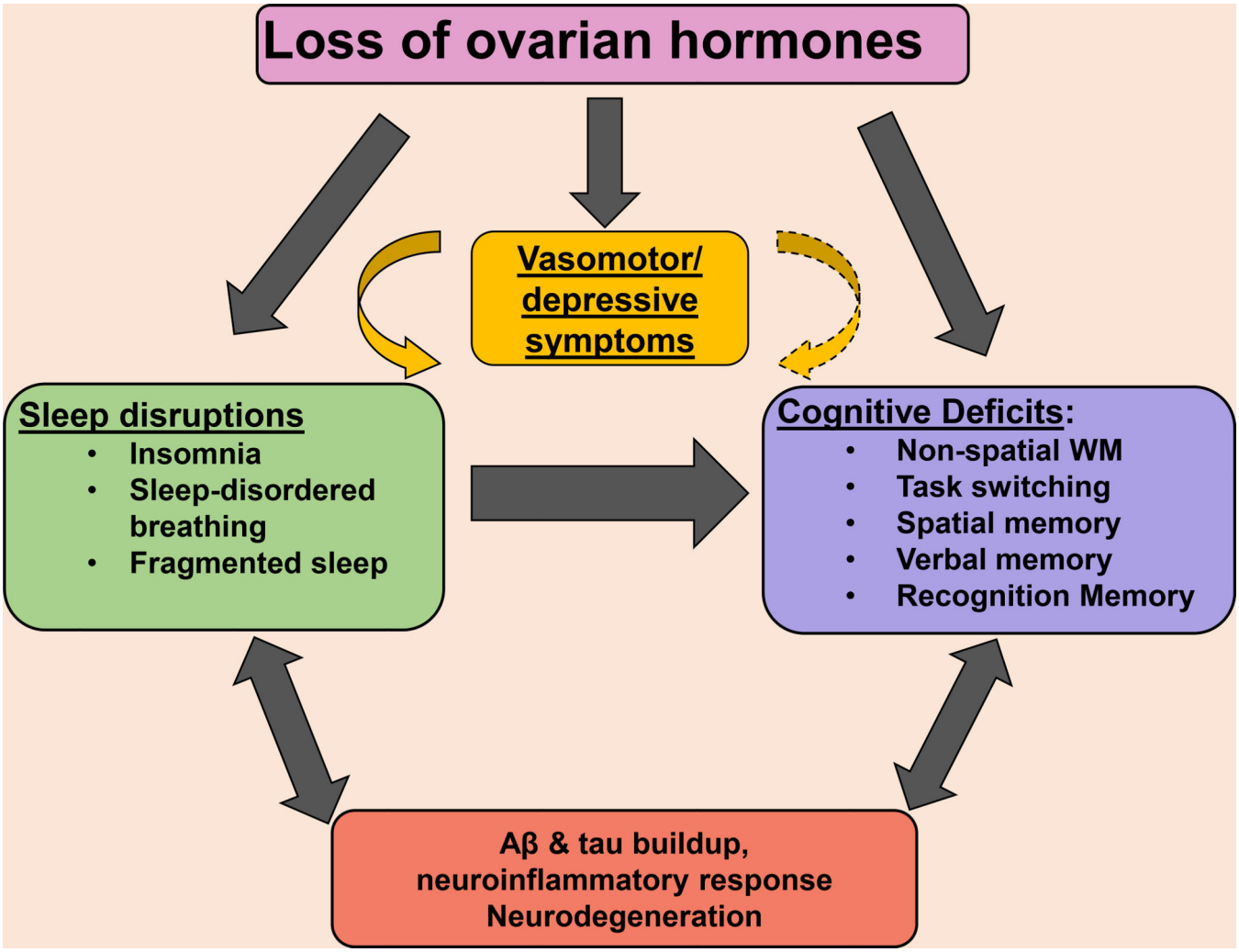

Figure 1.

Schematic model illustrating proposed effects of hormone deprivation resulting from menopause on sleep disruptions and selective cognitive deficits. Sleep disruptions may include reduced sleep quality/efficiency, or fragmented sleep, and in more severe cases, development of sleep disorders (i.e. insomnia or sleep disordered breathing). Since sleep is also known to modulate these cognitive abilities, it is proposed that loss of ovarian hormones can further exacerbate cognitive impairments via development of sleep disorders/fragmented sleep. There is some evidence that symptomatic women are more vulnerable. Extended periods of sleep disruptions could increase inflammation and synaptic damage leading to further cognitive deficits. Note: Aβ = β-amyloid; SDB = sleep-disordered breathing; WM = working memory.

Table 1.

Summary of the effects of ovarian hormones on cognition

Ability	Sample Characteristics	Younger	Older	References
Attention				
			Humans	
	Premenopause	F > L		Pletzer et al., 2014
	Postmenopause (55–65 years)		HRT > no HRT	Castonguay et al., 2015
	Postmenopause		HRT > no HRT	Fedor-Feyberg, 1977;
	Postmenopause (~60 years)		ERT > no ERT	Schmidt et al., 1996
	Postmenopause (~65 years)		HRT > no HRT	Smith et al., 2001
	Postmenopause (~53 years)		HRT = no HRT	Gleason et al., 2015
	Postmenopause (47–65 years)		ERT = no ERT	Polo-Kantola et al., 1998b
	Postmenopause (53–72 years)		HRT = no HRT	Alhola et al., 2006
	Postmenopause (~53 years)		HRT = no HRT	Keenan et al., 2001
	Postmenopause (58–75 years)		HRT = no HRT	Wolf et al., 2005
			Animals	
	OVX macaques (6–11 years)	OVX < intact E2 > vehicle		Voyko 2002
	OVX macaques (7–16 years)	E2 = Vehicle		Lacreuse et al., 2009
	OVX macaques (~20 years)		E2 > No E2	Voytko et al., 2009
	OVX macaques (18–25 years)		E2 > No E2	Kohama et al., 2016
	17-mo OVX rats		E2 > No E2	Bohacek & Daniel, 2010
	Intact rats	Proestrous < Estrous/Diestrous		Quinlan et al., 2010
		E2 < Vehicle		Almey et al., 2013
Non-spatial working memory				
			Humans	
Maintenance				
Digit Span forward:	Postmenopause		HRT = no HRT	Alhola et al., 2006; Castonguay et al., 2015; Duff & Hampson, 2000; Gleason et al., 2015; Keenan et al., 2001; Polo-Kantola et al., 1998b; Schmidt et al., 1996

Ability	Sample Characteristics	Younger	Older	References
Manipulation/Updating				
		Early F = Late F		Joseph et al., 2012
	Postmenopause (~56 years)		HRT > no HRT	Duff & Hampson, 2000
	Postmenopause (55–65 years)		HRT = no HRT HRT > no HRT	Castonguay et al., 2015
	Postmenopause (~53 years)		HRT = no HRT	Gleason et al., 2015
	Postmenopause (~53 years)		HRT > no HRT	Keenan et al., 2001
	Postmenopause (50–65 years)		3 days ERT > no ERT	Krug et al., 2006
	Postmenopause (~69 years)		HRT = no HRT	Janowsky et al., 2000
	Postmenopause (~70 years)		ERT > no ERT	Baker et al., 2012
			Animals	
Object-DRST *Face-DRST*	OVX macaques (6–9 years)	EE2 = no EE2 EE2 < no EE2		Lacreuse & Herndon, 2003
Object-DRST	OVX macaques (7–16 years)	EB = no EB		Lacreuse et al., 2009
	OVX rats	Low EB > no EB Mod-high EB < no EB		Wide et al., 2004
	OVX rats	High E2 < no E2		Wang et al., 2008
	OVX rats	High E2 < no E2	High E2 < no E2	Wang et al., 2009
Task switching				
			Humans	
	Premenopause	GnRHa = GnRHa + E/P GnRHa: ↓ DLPFC GnRHa + E/P: ↑ DLPFC		Berman et al., 1997
	Postmenopause (~60 years)		ERT > no ERT	Schmidt et al., 1996
	Postmenopause (55–65 years)		HRT > no HRT	Castonguay et al., 2015
	Early postmenopause (~52 years)		↑DLPFC in HRT users; correlated with performance	Girard et al., 2017
	Postmenopause (~65 years)		3-mo ERT = no ERT	Duka et al., 2000
			Animals	

Ability	Sample Characteristics	Younger	Older	References
	OVX macaques (~20 years)		HRT > no HRT	Voytko et al., 2009
	OVX macaques (~24 years)		EE2 = no EE2	Lacreuse et al., 2004
	Young OVX rats	E2 > no E2		Lipatova et al., 2016
reversal learning	OVX marmosets (3–5 years)		High E2 < No E2	Lacreuse et al., 2014
reversal learning	OVX rats (21–22 mo)		E2 < no E2	Gibbs et al., 2011
Response inhibition				
			Humans	
Go/No-Go, Stop-Signal	Premenopause	F < L		Colzato et al., 2010; Reimers et al., 2014
Stroop Interference	Postmenopause (50–65 years)		3 days ERT > no ERT	Krug et al., 2006
Stroop Interference	Postmenopause		HRT = no HRT	Alhola et al., 2006; Baker et al., 2012; Castonguay et al., 2015; Duka et al., 2000; Polo-Kantola et al., 1998b; Wolf et al., 2005
			Animals	
Stop Signal	Premenopausal baboons	O = L		Lacreuse et al., 2016
DRL	OVX rats	High E2 < no E2		Wang et al., 2008
DRL	OVX rats	High E2 < no E2	E2 = no E2	Wang et al., 2011
Decision making				
			Humans	
	Premenopause & postmenopause (~55 years)	Menses = mid L	ERT = no ERT	Reavis & Overman, 2001
	Premenopause	F > menses		Smith et al., 2014
			Animals	
	OVX rats	High EB > no EB		Uban et al., 2012
Spatial Working Memory				
			Humans	
	Premenopause	High E2 > Low E2 E2 correlates with performance		Hampson & Morley 2013
	Postmenopause (~56 years)		HRT > no HRT	Duff & Hampson, 2000

Ability	Sample Characteristics	Younger	Older	References
	Postmenopause (~71 years)		3-mo ERT = no ERT	Schiff et al., 2005
		Animals		
	Premenopause	O < F=L		Lacreuse et al., 2001
	OVX macaques (6–9 years)	EE2 = no EE2		Lacreuse et al., 2003
	OVX macaques (7–16 years)	E2 = Vehicle		Lacreuse et al., 2009
	Macaques (6–10 years)	OVX = intact E2 = no E2		Voytko, 2000
	Macaques (~ 10 years)	E2 = no E2		Hao et al., 2007
	Macaques (20–27 years)		Premenopause > peri/ postmenopause	Roberts et al., 1997
	OVX macaques (~22 years)		E2 > no E2	Rapp et al., 2003
	OVX macaques (18–25 years)		E2 > E2/P > No E2	Kohama et al., 2016
	OVX macaques (21–24 years)		EE2 > no EE2	Lacreuse et al., 2002
	OVX macaques (~20 years)		E2 = E2/P = no E2	Voytko et al., 2008
	OVX marmosets (3–5 years)		High E2 < No E2	Lacreuse et al., 2014
	OVX macaques (19–27 years)		Long-term OVX > intact	Lacreuse et al., 2000
	Intact rats	Proestrous > estrous		Pompili et al., 2010
	OVX rats	E2 > no E2		Gibbs, 2007; Holmes et al., 2002; Luine et al., 1998; Sandstrom & Williams, 2001; Velàzquez-Zamora et al., 2012
	OVX rats	Win-stay: E2 = no E2 Win-shift: E2 < no E2		Galea et al., 2001
	OVX rats	Intra-PFC/HPC E2 > vehicle		Sinopoli et al., 2006
	12-mo old OVX rats		E2 > no E2	Daniel et al., 2006
	21–25-mo old OVX rats		E2+P > no E2+P	Gibbs, 2000
	13–22-mo old OVX rats		OVX < intact E2 > no E2	Markowska & Savonenko, 2002
Spatial reference memory				
		Animals		
	Intact rats	Proestrous = estrous		Berry & McMahan, 1997;

Ability	Sample Characteristics	Younger	Older	References
	Intact rats	Watermaze: Proestrous < estrous RAM: Proestrous = estrous		Pompili et al., 2010
		Proestrous < estrous		Warren & Juraska, 1997
	OVX rats	Watermaze: E2 > no E2 Y-maze: E2 = no E2		McLaughlin, 2008
		E2 > no E2 Intra-HPC E2 > vehicle		Packard & Teather, 1997a,b
	OVX rats	E2 < no E2		Galea et al., 2001
	OVX rats	E2 = no E2		Fader et al., 1999; Holmes et al., 2002; Luine et al., 1998;
	4, 16, & 24-mo old OVX rats	E2 > no E2	E2 = no E2	Talboom et al., 2008
	13–22-mo old OVX rats		OVX = intact E2 = no E2	Markowska & Savonenko, 2002
Object placement/NOIP test				
		Animals		
	OVX rats	E2 > no E2		As reviewed by Tuscher et al., 2014; McLaughlin et al., 2008
Spatial strategy				
		Humans		
	Premenopause	Late L > Early F/O		Hussain et al., 2016
		Animals		
	Rats	Proestrous > estrous E2 > no E2	E2 > no E2	As reviewed by Korol & Pisani, 2015; Korol et al., 2004
	OVX rats	Intra-HPC E2 > Vehicle		Zurkovsky et al., 2007
Verbal memory				
		Humans		
	Premenopause	Inconsistent reports, or F = L = Menses		As reviewed by Poromaa & Gingnell, 2014
	Premenopause	GnRHa < cycling		Craig et al., 2008
		GnRHa = cycling		Guerrieri et al., 2016; Owens et al., 2002

Ability	Sample Characteristics	Younger	Older	References
	Age: ~45–52 years		Peri-/postmenopause/ < premenopause	Greendale et al., 2009; Weber et al., 2013
	Surgically menopausal women (36–45 years)		BL > post-surgery	Sherwin, 1988
	Postmenopause		HRT > no HRT	Baker et al., 2012; Castonguay et al., 2015; Jacobs et al., 1998; Kampen & Sherwin, 1994; Keenan et al., 2001; Maki, Zonderman, & Resnick, 2001; Phillips & Sherwin, 1992b; Resnick et al., 1998
	Postmenopause		HRT = no HRT	Baker et al., 2012; Gleason et al., 2015; Henderson et al., 2016
Visual recognition memory				
			Humans	
	Premenopause	GnRHa < cycling		Craig et al., 2010
	Postmenopause (~65–67 years)		ERT > no ERT	Resnick et al., 1998
	Postmenopause (~64 years)		HRT = no HRT	Alhola et al., 2006
	Older AD patients (~74 years)		ERT = no ERT	Sundermann et al., 2006
			Animals	
	Premenopause	No/brief retention delay: F = L 30-s retention delay: O < F=L		Kromrey, Czoty, & Nader, 2015; Lacreuse et al., 2001
	OVX macaques (6–9 years)	EE2 = no EE2		Lacreuse & Herndon, 2003
	OVX macaques (7–16 years)	E2 = Vehicle		Lacreuse et al., 2009
	OVX macaques (~20–24 years)		HRT > no HRT	Lacreuse et al., 2002; Rapp et al., 2003; Voytko et al., 2008
	OVX rats with low E2	Intra-PRh E2 < vehicle		Gervais et al., 2013, 2016
Novel object preference				
	Rats	Proestrous > estrous E2 > no E2 Intra-HPC > vehicle Intra-PRh > vehicle	Intra-HPC E2 = vehicle	As reviewed by: Galea, Frick, Hampson, Sohrabji, & Choleris, 2016; Luine, 2015; Tuscher et al., 2014

Note: AD = Alzheimer's Disease; DLPFC = dorsolateral prefrontal cortex; DRST = delayed recognition span test; E2 = 17β-estradiol; EB = estradiol benzoate; EE2 = ethinyl estradiol; ERT = estrogen replacement therapy; F = follicular phase; GnRHa = gonadotropin releasing hormone agonist; HPC = hippocampus; HRT = hormone replacement therapy; L = luteal; mo = month; O = Ovulatory; P = progesterone; PRh = perirhinal cortex; OVX = ovariectomized.

Table 2.

Summary of the effect of sleep loss on cognition

Ability	Sample Characteristics	Younger	Older	References
Attention				
		Humans		
	Meta-analysis	Deficits seen after 24–48 hr SD		As reviewed by Lim & Dinges, 2010
	Mixed sex (~20 years)	1 night PSR < no restriction		Rossa et al., 2014
	Young (~22 years) & old (~66 years) men	Young more impaired than older after 40 hr SD		Adam et al., 2006
	Young (~21 years) & old (~66 years) mixed-sex	Young more impaired than older after 24 hr SD		Duffy et al., 2009
	Young (~23 years) & older (~66 years) men	Young more impaired than older after 40 hr SD		Sagaspe et al., 2012
		Animals		
	Age & sex not indicated	24 hr SD < BL		Christie et al., 2008
	Male rats (~2-mo old)	28 hr PSR < BL 58–148 hr PSR = BL		Deurveilher et al., 2015
	Male rats	4–10 hr SD < no SD		Córdova et al., 2006
Non-spatial working memory				
		Humans		
	Meta-analysis	Deficits seen after 24–48 hr SD		As reviewed by Lim & Dinges, 2010
	Mixed-sex (22–38 years)	51–54 hr SD = BL		Tucker et al., 2010, 2011
Task switching				
		Humans		
	Patients with sleep-related breathing disorders < controls			As reviewed by Fulda & Schulz, 2003
	Mixed sex (~21 years)	34–36 hr SD = controls		Binks et al., 1999
	Mixed sex (18–23 years)	5 days PSR < BL		Herscovitch et al., 1980
	Male (19–32 years)	1 night SD increases shift cost		Heuer et al., 2004
	Mixed sex (~22 years)	1 night SD impairs preparatory bias		Jennings et al., 2003
		Animals		

Ability	Sample Characteristics	Younger	Older	References
	Young male rats	3/24 hr fragmented sleep < controls		McCoy et al., 2007
Response inhibition				
		Humans		
	Mixed sex (~24 years)	23/32/55 hr SD < BL		Drummond et al., 2006
	Mixed sex (~37 years)	4 nights of PSR < control		Demos et al., 2016
	Young (~23 years) & older (~66 years) men	40 hr SD < BL for both groups equally		Sagaspe et al., 2012
	Mixed sex (~20 years)	1 night PSR = no restriction		Rossa et al., 2014
		Animals		
	Male rats	7 days of PSR < BL		Kamphuis et al., 2016
	3-mo old male rats	SD < sleep		Borquez et al., 2014
Decision making				
		Humans		
	Mixed sex (~25 years)	49/75 hr SD < BL		Killgore et al., 2006, 2007
	Mixed sex (~21 years)	1 night SD < Rested		Fraser et al., 2013
	Mixed sex (~25 years)	51 hr SD = BL 75 hr SD < BL		Killgore et al., 2011
	Male (18–28 years)	36 hr SD < RW		Lei et al., 2016
	Mixed sex (~20 years)	1 night PSR < no restriction		Rossa et al., 2014
	Mixed sex (~37 years)	4 nights of PSR = control		Demos et al., 2016
	Review	Some complex tasks: SD = control		As reviewed by Harrison & Horne, 1980
	Review	Majority of studies: SD < control 5 studies: SD = control		As reviewed by Womack et al., 2013
	Mixed sex (18–30 years)	ED: 1 night SD < RM DD: 1 night SD < RM		Libedinsky et al. 2013,
Spatial memory				
		Humans		
	Male (18–30 years)	HPC activity during SWS resembled patterns during encoding of learning task		Peigneux et al., 2004
	Mixed sex (20–30 years)	SWS and not REM involved in spatial memory consolidation		Rasch et al., 2007

Ability	Sample Characteristics	Younger	Older	References
		Animals		
	9-mo old male rats	HPC activity during SWS resembled patterns during encoding of novel environment		Wilson & McNaughton, 1994
	Female macaques (19–25 years)	4 hr PSD	Performance negatively related to sleep latency/ wake bouts	Haley et al., 2009
	Male mouse lemurs (2–3 years)	Spatial learning: 8 hr SD = control Spatial retrieval: 8 hr SD < control		Rahman et al., 2013
	Male rats (6–7 mo old)	Reference memory: 4 hr PSD 0–4 hr post-learning < control Working memory: 4 hr PSD 0–4 hr post-learning = control		Smith et al., 1998
	Male rats	Reference memory: 24 hr sleep fragmentation < controls Working memory: 24 hr sleep fragmentation = controls		Ward et al., 2009
	Male rats	Working memory: 5–7 days of intermittent hypoxia < controls		Row et al., 2007
	Male rats (1–1.5 mo)	4 hr SD immediately post-learning < control 4 hr SD 4–8 hr post-learning = controls		Ishikawa et al., 2014
	Male rats	Sleep following encoding enhances spatial memory		Inostroza et al., 2013
	Male mice	6 hr SD immediately post-learning = control 6 hr SD 4–8 hr post-learning = controls		Palchykova et al., 2006
Verbal memory				
		Humans		
	21–35 years, sex not indicated	Free recall: 35 hr SD < rested state Recognition: 35 hr SD = rested state		Drummond et al., 2000
	Mixed sex (~61 years) sample with obstructive sleep apnea		No association between objective sleep and word recall	Lutsey et al., 2016
	Mixed sex (~23 years)	Sleep immediately after learning > wake		Sheth et al., 2012

Ability	Sample Characteristics	Younger	Older	References
	18–22 years. Sex unspecified	Sleep immediately after learning > wake		Ellenbogen et al., 2009
	Female (~53 years)		Sleep duration & HFs predict delayed LM, but not CVLT	Maki et al., 2008
	Mixed sex sample (20–30 years)	Recollection: SWS > REM Familiarity: SWS = REM		Daurat et al., 2007
	Mixed sex sample (19–28 years)	Recollection: SWS > wake Familiarity: SWS/REM = Wake		Drosopoulos et al., 2005
	University students. Age & sex unspecified	Sleep immediately post learning = Delayed sleep		Nesca & Koulak, 1994
Visual recognition memory				
		Humans		
	Mixed sex (~22 years)	1 night SD < control		Mograss et al., 2009
	Mixed sex (18–36 years)	1 night SD < control		Acheson et al., 2007
		Animals		
	Male rats (1–1.5 mo)	4 hr SD immediately post-learning = control 4 hr SD 4–8 hr post-learning = controls		Ishikawa et al., 2014
	Male mice	6 hr SD immediately post-learning < control 6 hr SD 4–8 hr post-learning = controls		Palchykova et al., 2006

Note: BL = baseline; CVLT = California verbal learning test; DD = delay discounting; DLPFC = dorsolateral prefrontal cortex; DRST = delayed recognition span test; ED = effort discounting; HF = hot flash; hr = hour; LM = Logical memory; mo = month; PSD = paradoxical sleep deprivation; PSR = partial sleep restriction; SD = sleep deprivation; REM = rapid-eye movement; RW = rested wakefulness; SOP = self-ordered pointing test; SWS = slow-wave sleep.