



## Review article

## Sex differences in sleep and sleep loss-induced cognitive deficits: The influence of gonadal hormones

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## ABSTRACT

Males and females can respond differentially to the same environmental stimuli and experimental conditions. Chronic sleep loss is a frequent and growing problem in many modern societies and has a broad variety of negative outcomes for health and well-being. While much has been done to explore the deleterious effects of sleep deprivation (SD) on cognition in both human and animal studies over the last few decades, very little attention has been paid to the part played by sex differences and gonadal steroids in respect of changes in cognitive functions caused by sleep loss. The effects of gonadal hormones on sleep regulation and cognitive performances are well established. Reduced gonadal function in menopausal women and elderly men is associated with sleep disturbances and cognitive decline as well as dementia, which suggests that sex steroids play a key role in modulating these conditions. Finding out whether there are sex differences in respect of the effect of insufficient sleep on cognition, and how neuroendocrine mediators influence cognitive impairment induced by SD could provide valuable insights into the best therapies for each sex. In this review, we aim to highlight the involvement of sex differences and gonadal hormone status on the severity of cognitive deficits induced by sleep deficiency in both human and animal studies.

## 1. Introduction

Sleep is a behavior observed in most organisms, and in homeothermic vertebrates, is a highly evolved behavioral state which is defined by characteristic changes in posture, diminished muscle tone, and increased sensory threshold coincident with distinctive brain electrical activity (Chokroverty, 2017; Schwartz and Kilduff, 2015). There are at least two regulatory mechanisms for sleep-wake cycles; biological clocks (i.e. circadian rhythms), which signal the timing of sleep over a 24 h cycle, and homeostatic drive, or the need for sleep, which increases correspondingly with the time spent awake (Borbély, 1982). Cortical activity during the sleep/wake cycle can be traced using electroencephalography (EEG) and used to classify three different vigilance states. These states are (1) wake, characterized by low amplitude, high frequency EEGs, (2) rapid-eye movement (REM) sleep, with EEGs similar to those of wake (paradoxical sleep), and (3) non-rapid eye movement (NREM) sleep, which is further divided into three stages (N1–N3). The deepest stage, N3, is also known as slow-wave sleep (SWS), determined by the predominance of low frequency, high amplitude EEGs (i.e. delta waves). The sleep-wake cycle characteristically

progresses from wake, to the first (lightest) stage of NREM (N1), then to deeper stages (N2–N3) before transition to REM sleep. In healthy adult humans, each cycle takes about 90 min, with a total of three to five cycles per night (McKenna et al., 2017; Porkka-Heiskanen, 2013).

Despite the relatively good understanding of sleep behaviour and mechanisms, the exact functional significance of sleep remains enigmatic. In our view, the best supported hypothesis is that sleep serves as a restorative mechanism for the body, counteracting the waste products accumulated during wakefulness (Assefa et al., 2015; Siegel, 2005). Adequate sleep duration requirements differ across the lifespan and from person to person (Hirshkowitz et al., 2015). Over the previous century, typical sleep time per 24 h has decreased by 1.5 h and this trend seems to be continuing (Matricciani et al., 2017; Rajaratnam and Arendt, 2001). Chronic sleep loss is a frequent and growing problem in many modern societies and is a risk factor for a broad variety of disorders (Tufik et al., 2009), from psychological (Okun et al., 2018; Pires et al., 2016; Pires et al., 2015), neurological (Chokroverty and Nobili, 2017; Pasic et al., 2011) and neurodegenerative disorders (Musiek et al., 2015; Olsson et al., 2018), to metabolic and cardiovascular diseases (Joukar et al., 2013; Liu et al., 2016; Shan et al., 2015). It is well

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established in the literature that sleep disruption or extended wakefulness in humans can interfere with almost all cognitive processes (Bubu et al., 2017; Lo et al., 2016). Deficits in both declarative and non-declarative memory, attention, executive function, as well as emotional reactivity and sensory perception have been reported following sleep deprivation (Gunzelmann et al., 2012; Lowe et al., 2017; Walker, 2008). The effects of sleep loss on various cognitive tasks and corresponding molecular and cellular mechanisms have also been documented in many rodent studies. Total sleep deprivation (TSD), paradoxical sleep deprivation (PSD) and sleep fragmentation (SF), are the most common types of sleep loss examined in experimental models, and are frequently used in rodent studies to address the correlation between sleep and cognitive performance (McCoy and Strecker, 2011). Sleep loss induced by all these models has been shown to lead to impairment in hippocampal-dependent memory (Hajali et al., 2012; Prince et al., 2014; Saygin et al., 2017; Tartar et al., 2006) as well as changes in cellular and molecular correlates involved in membrane excitability and synaptic plasticity within the hippocampus (Havekes et al., 2016; Kreutzmann et al., 2017; Prince et al., 2014; Tartar et al., 2006).

There are sex differences at all levels of the central nervous system, including at genetic, system and behavioral levels (Cahill, 2006; Jazin and Cahill, 2010). Aspects of learning and memory, as well as, sleep patterns and quality are quite different between the sexes (Keeley et al., 2015; Mong et al., 2011; Saylik et al., 2018). Some sleep-related disorders also vary in severity and prevalence in male and females. Based on clinical evidence, narcolepsy, REM sleep behaviour disorder and obstructive sleep apnoea are more common in men, while insomnia and restless leg syndrome are more common in women (Mallampalli and Carter, 2014; Shaib and Attarian, 2017; Silva et al., 2008).

There are some studies suggesting that sex differences and the stage of menstrual cycle affect the beneficial effects of sleep in respect of memory consolidation (Genzel et al., 2012; McDevitt et al., 2014; Sattari et al., 2017). One study explored the effects of a nap on memory consolidation of motor and verbal skills in healthy males, and females during the early-follicular and mid-luteal phases of the menstrual cycle (Genzel et al., 2012). The findings showed a sex, and in women, a menstrual cycle effect on memory function following a nap. Men functioned significantly better after a nap but women only did so in the mid-luteal phase. Only the men and mid-luteal women experienced a significant increase in spindle activity after learning (Genzel et al., 2012).

Another study investigated differences between men and women in offline consolidation of perceptual learning (PL) of motion direction discrimination after a nap (McDevitt et al., 2014). The results showed that REM sleep facilitates consolidation of PL but that the pattern of REM-induced facilitation differed between men and women. REM sleep in the men was highly specific to the trained direction of motion, whereas in the women it resulted in generalized learning of the untrained direction and the novel direction (McDevitt et al., 2014). These findings demonstrate that sleep-related memory consolidation may be sex dependent. Furthermore, studies addressing the ovarian cycle effect on sleep-dependent memory consolidation in women conclude that the positive association of sleep and cognition is more profound in high-hormone menstrual phases, compared with low-hormone phases (Baker et al., 2018b).

Additionally, it seems that the adverse effects of sleep deficiency may be different between men and women. For example, it has been reported that self-reported general functioning is better in men than in women during the day following less than 7 h of sleep (58% vs. 43%) (Drake et al., 2005). Regarding the psychological consequences of sleep loss, a longitudinal study of bipolar disorder indicated that poor sleep quality was a strong predictor of the severity, variability and frequency of episodes of depression and mania in women but not in men (Saunders et al., 2015). Another study which monitored the effects of SD on some specific forms of impulsive behaviour in healthy men and women volunteers indicated that it did not affect most measures of

impulsive behavior. However, it decreased risk taking in women, but not in men (Acheson et al., 2007). The association between inadequate sleep duration and hypertension, weight gain, and obesity is well established in both men and women, but it may be stronger among women (Grandner et al., 2018; Makarem and Aggarwal, 2017). In the case of the pro-inflammatory effects of sleep loss, women also seem to be more affected than men (Miller et al., 2009; Prather et al., 2013). One study reported that whereas both females and males showed a marked increase in the cellular markers of inflammation on the morning immediately after a night of sleep loss, production of pro-inflammatory cytokines during the early and late evening was increased in the females while it decreased in the males (Irwin et al., 2010). In respect of other consequences of sleep loss however, men may show more susceptibility to the effects of SD. Alkozei et al. reported that after chronic sleep restriction men showed a significant decline in their tendency towards low-calorie foods, whereas women did not show a significant change (Alkozei et al., 2017). Therefore, sleep-deprived men may be at increased risk of weight gain due to a reduced bias towards low-calorie foods. This evidence suggests that there are robust sex differences in the clinical symptoms and negative outcomes of sleep deficiency.

These findings may be due to structural differences in the brain which take place during a critical developmental time window when sex steroids masculinize and feminize the neural substrates, whereas the absence of sex steroids results in a feminization process (McCarthy and Nugent, 2015). In adulthood, the synthesis and release of sex steroids from the gonads activate these differentiated neural circuitries resulting in specific behaviours appropriate to the biological sex of the animals. This two-step process of developmental and adult exposure to sex steroids is typically denoted as the organizational/activational hypothesis (Arnold, 2009). Several independent sex-specific factors, hormonal, genetic and epigenetic, act in parallel to induce or eliminate sex differences in the brain and other tissues which ultimately lead to the functional differences between the sexes (Arnold, 2017; McCarthy and Arnold, 2011; Wolstenholme et al., 2013). The hypothesis suggests that sex differences in neuronal development are regulated by the interaction of sex chromosomes, gonadal and neuronal derived steroids (Cambiaso et al., 2017). Sex differences in sleep behaviours and circadian rhythms and the mechanisms governing these differences appear, in part, to be dependent on organizational and activational effects of steroid hormones (Brockman et al., 2011; Cusmano et al., 2014; Mong and Cusmano, 2016). However, as discussed in the following sections, in addition to the hormonal effects, a complicated story of several independent sex-specific factors, including genetic and epigenetic paradigms have been suggested to contribute to the establishment of sex differences in sleep.

While there has been a lot of work done to explore the impairing effects of SD on cognition in both human and animal studies over the last few decades, very little attention has been paid so far to the role of sex differences and gonadal steroids in the susceptibility of subjects to the deleterious effects of sleep loss on cognitive functions. Understanding how the two sexes respond to the negative effects of sleep loss on cognition, and how neuroendocrine mediators influence cognitive impairments induced by SD could provide valuable insights into the best therapies for each sex.

The objective of this review is to examine the involvement of sex differences and gonadal hormone status in sleep homeostasis and in the severity of cognitive deficits induced by sleep deficiency in both human and animal studies.

### 1.1. Sex differences and gonadal hormone influence on sleep and homeostatic response to sleep loss

Objective polysomnographic (PSG) evaluation of healthy subjects to explore sex differences in sleep and sleep architecture have shown mixed results. However, there is a common finding across these studies

that women, in general, sleep objectively better than men (Bixler et al., 2009; Shambroom and Fabregas, 2010). PSG data showed that total sleep time is significantly longer, sleep onset latency is shorter and sleep efficiency is better in women than men (Goel et al., 2005; Roehrs et al., 2006). Similarly, a cross-sectional analysis (Redline et al., 2004) reported that compared with women of matched ages, men had lighter sleep. Another consistency across the studies considering sex differences is that women show greater slow wave activity (SWA), a measure of sleep intensity during slow wave sleep, at all ages and it is less influenced by aging than it is in men (Carrier et al., 2001; Ehlers and Kupfer, 1997; Mongrain et al., 2005). As sleep is closely linked to circadian timing, the established differences in circadian timing and sleep behavior between men and women may be a contributing factor. Women tend to go to bed earlier and wake up earlier than men from childhood to menopause, at which time the differences disappear (Tonetti et al., 2008). A study by Boivin et al. examined the diurnal and circadian rhythms of sleep and alertness in men vs. naturally cycling women (Boivin et al., 2016). They found that, compared with men, women demonstrated an advance in the diurnal and circadian variation of sleep measures and subjective alertness, as well as a significant phase advance of the core body temperature. Furthermore, women displayed an increased in amplitude of the diurnal and circadian variation of alertness, predominantly due to a larger decline in the nocturnal nadir. Lower night-time alertness is also observed in this study, suggesting a physiological basis for a greater vulnerability to maladaptation to night shift work in women (Boivin et al., 2016). The Difference in circadian timing can differentially influence the capability of men and women to adapt to shift work and jetlag (Bailey and Silver, 2014; Yan and Silver, 2016).

Despite this objectively better sleep quality, healthy women across a wide range of ages report more sleep problems. In subjective assessments and self-evaluations, women report interrupted and insufficient sleep more frequently than men (Reyner and Horne, 1995; Suh et al., 2018; Yoshioka et al., 2012; Zhang and Wing, 2006). Difficulties falling asleep, repeated awakenings, longer periods of time awake throughout the night and generally poorer sleep quality are the most commonly reported problems in women (Zhang and Wing, 2006). It is unclear what underlies this discrepancy between the objective and subjective sleep observations in women, but it can, in part, be due to some sleep independent factors such as ovulatory cycles and premenstrual mood fluctuations (Baker and Lee, 2018; Ozisik Karaman et al., 2012). In a PSG sleep study of premenstrual women (Baker et al., 2012), poorer subjective sleep quality correlated with higher levels of anxiety and depressive symptoms in the absence of any objective sleep disturbances, suggesting that subjective sleep quality evaluations are strongly affected by these factors. Hachul's group has shown that although early menopause was associated with a range of symptoms, sleep complaints were higher in the late post-menopausal group. However, polysomnographic findings revealed no significant differences between early and late postmenopausal women (Hachul et al., 2009). Additionally, it was shown by the same group that while hormone therapy decreased the prevalence of sleep disturbances in postmenopausal women, it had no significant improving effect (only a trend towards improvement) on objective sleep quality (Hachul et al., 2008).

Evidence suggests that following SD, women show greater SWA rebound, suggesting that sleep debt may accumulate more quickly in women and may have greater debilitating impacts, leading to the assumption that there are sex differences in the ability to recover from sleep loss (Armitage et al., 2001). A study by Corsi et al. tested the effect of 38 h of total sleep deprivation on the waking EEG in women and concluded that women need more sleep than men to recover (Corsi-Cabrera et al., 2003). The difference in the accumulation and dispersion rates of sleep pressure between men and women may be responsible for sex differences in SWA responses following SD and in objective and subjective sleep quality. It seems that the detrimental effects of sleep loss on health outcomes are more profound in women than men. There

are studies showing that women are more vulnerable to developing cardiovascular and metabolic disorders due to sleep restriction (Cappuccio et al., 2007; Makarem and Aggarwal, 2017; Miller et al., 2009). Ferrara et al. assessed the effects of one night of SD on subjects' risk and social preferences in male and female university students (Ferrara et al., 2015). After sleep loss, males made riskier decisions, while females' reaction to SD was characterized by decreased risky choices and increased egoism compared to males (Ferrara et al., 2015). These results show that one night of SD alters economic behavior in a gender-specific manner. The differential responses of the two sexes may be attributed to intrinsic psychological gender differences, such as how men and women evaluate possibilities in their decision-making, and/or to the different neurophysiological correlates of decision-making processes. Regarding the cognitive effects of SD on the two sexes, the findings in respect of humans and rodents are discussed in the following sections (Baratta et al., 2018b; Fernandes-Santos et al., 2012; Hajali et al., 2012; Rangtall et al., 2018).

Sleep and sleep architecture in rodents are also sexually dimorphic. In general, male rodents spend more time in sleep states than females (Paul et al., 2006). A study of sleep architecture in mice suggested that in comparison to baseline levels, females exhibit a more robust recovery response (Paul et al., 2006). Moreover, NREMS delta power, which is analogous to SWA in humans, is higher in female mice during baseline and recovery sleep. In this study, gonadectomy in both sexes reduced or eliminated the majority of sex differences in sleep architecture and homeostasis (Paul et al., 2006). The homeostatic sleep responses to environmental stimulation can also be sex dependent in rodents. A study in mice showed that in contrast to the similar homeostatic recovery responses to 6 h of SD, male and female mice showed markedly different changes in sleep after one-hour of restraint stress (Koehl et al., 2006). In fact, males displayed a stronger initial suppression of sleep and a stronger rebound of REM sleep later in the recovery phase, suggesting the existence of sex differences in sleep responses to stress (Koehl et al., 2006). In rats exposed to SD, females in different oestrus cycles and males were shown to display distinct patterns of sleep rebound architecture (Andersen et al., 2008).

As for some neurobehavioral functions, the reported sex differences in sleep architecture and sleep homeostatic responses may also be in part due to the influence of sex hormones. Old and new evidence from both human (Ballinger, 1976; Lord et al., 2014) and animal (Branchey et al., 1971; Cusmano et al., 2014) studies suggests that gonadal hormones in females, and to a lesser extent in males, have a significant effect on sleep-wake cycles. There are studies showing that the amplitude of activity, free-running time and daily rhythms are also influenced by gonadal steroids in both male and female rodents (Davis et al., 1983; Karatsoreos and Silver, 2007; Mong et al., 2011). Basic clinical studies have provided further evidence of the influence of gonadal steroids in sleep homeostasis and circadian timing (Baker and Lee, 2018).

A general conclusion derived from the current literature focusing on the effects of sex steroids on sleep is that sleep in females seems to be more influenced by gonadal hormone fluctuations. In agreement with this, Cusmano et al. demonstrated that the changes in sleep behavior induced by either estradiol or testosterone were greater in female rats compared with males, suggesting that sleep behavior in females is more sensitive to the effects of gonadal steroids (Cusmano et al., 2014). Sleep complaints mainly coincide with specific periods and events in women's lives, such as puberty, the menstrual cycle, pregnancy and menopausal transition in which there are marked fluctuations in ovarian steroids (Baker and Driver, 2007; Baker and Lee, 2018; Freeman et al., 2015; Sedov et al., 2018). Regarding sleep changes during the menstrual cycle, it is established that the most dramatic changes occur during the post-ovulatory luteal phase when both estradiol and progesterone levels are high, compared to the follicular phase, when progesterone levels are low (Baker and Driver, 2007; Lord et al., 2014; Romans et al., 2015; Zheng et al., 2015). One study which objectively measured sleep in

women reported increased awakenings and arousal and decreased non-REM sleep during the luteal versus the follicular phase (de Zambotti et al., 2015). Moreover, the non-REM sleep spindles displayed a clear increase in EEG frequency range, number and duration in the luteal compared with the follicular phase (de Zambotti et al., 2015). A potential interaction between progesterone metabolites and GABA-A receptors is a plausible explanation for the increased spindle frequency activity observed in this study (Lancel et al., 1996).

The menopausal transition is a period in women's lives in which ovarian hormone fluctuations significantly influence sleep homeostasis and circadian rhythms. Disrupted sleep quality is one of the most frequent complaints in the menopausal transition, being reported by 33–51% of women, and there is a growing incidence of insomnia (Baker et al., 2018a; Lampio et al., 2017; Polo-Kantola, 2008). Hormone replacement therapy (HRT), a promising treatment for the symptoms of menopause, has also been reported to improve sleep quality, further suggesting a role for ovarian hormones in sleep (Cintron et al., 2017).

Unlike the well documented effects of gonadal steroids on sleep in women, the influences of sex hormones, mainly testosterone, in men are not so clear. Plasma testosterone levels are closely related to sleep cycles, with peak levels occurring just before or after REM sleep onset (Wittert, 2014a, 2014b) with disrupted sleep inhibiting the nocturnal increase in testosterone (Jauch-Chara et al., 2013). There is inconsistency in the evidence concerning the association between fluctuations in testosterone levels and sleep quality in men, with some studies reporting an association between lower testosterone and nocturnal awakenings, less time in SWS and decreased sleep efficiency (Barrett-Connor et al., 2008), while others conclude that testosterone replacement in older men or androgen administration in healthy young men are associated with poorer sleep efficiency and less total sleep time (Liu et al., 2003; Venâncio et al., 2008). In 2011, a study showed that there is an association between endogenous testosterone and sexual function, sleep and sleep disturbances, both in clinical trials as well as in animal model studies (Andersen et al., 2011). Indeed, sleep disturbance reduces testosterone levels in males (Andersen et al., 2010; Cote et al., 2013; Leproult and Van Cauter, 2011; Ukraintseva et al., 2018), and low sex steroid hormone concentrations have been associated with sexual dysfunction. The interaction between male sex hormones and sleep-related breathing problems supports the notion that these hormones play an important role in sleep disorders (Andersen and Tufik, 2008; Killick et al., 2013; Kim and Cho, 2018). A better understanding of the intricate relationships between sex steroid hormones, sleep/sleep disorders and sexual function could have important clinical implications.

The possible role of gonadal steroids in sex differences in sleep architecture and homeostatic sleep responses is also evidenced from animal studies. Some of the reported sex differences in sleep behavior and architecture have been shown to be eliminated in the absence of gonadal hormones (Koehl et al., 2006; Paul et al., 2006). Studies using ovariectomy with subcutaneous implant of ovarian hormones in rats that stabilizes plasma hormone levels for about two weeks have shown that estradiol alone, or in combination with progesterone, increases arousal and decreases spontaneous non-REM sleep and REM sleep in the active (dark) phase (Deurveilher et al., 2011). Similarly, both REM and non-REM sleep are significantly reduced in the pro-estrus phase, when estradiol and progesterone levels are high, compared to the other phases of the oestrous cycle of rats (Kleinlogel, 1983). The findings from existing studies suggest that sex hormones could be responsible, at least in part, for sex differences in sleep architecture and homeostatic sleep responses (Mong et al., 2011; Mong and Cusmano, 2016).

While many observed sex differences in sleep have been shown to be dependent on circulating gonadal hormones, several differences in circadian rhythms, sleep patterns and sleep regulatory mechanisms between the sexes appear to go beyond gonadal hormones and rely on inherent sex differences (Chen et al., 2015; Ehlen et al., 2013; Kuljis et al., 2013; Mong et al., 2011). The four core genotype (FCG) mouse

model which comprises XX and XY gonadal male and XX and XY gonadal female mice has enabled studies to test if sex differences in the sleep-wake cycle are caused by sex chromosome complement (SCC) or gonadal hormones or both (Arnold and Chen, 2009). This mouse line has been successful in revealing the contribution of sex chromosomes and gonadal hormones to the number of neuroanatomical phenotypes (Arnold and Chen, 2009), habitual responses to alcohol reinforcement (Barker et al., 2010) and agonistic and asocial behaviours (McPhie-Lalmansingh et al., 2008). Using this mouse model for revealing the effects of genetic sex and phenotypic sex interactions on sleep-wake regulation, Ehlen et al. showed that following forced wakefulness (6 h of forced wakefulness), XY females slept more during the mid-active phase (ZT 18–20) siestas than XX females and had higher NREM slow wave activity, a marker of sleep propensity, suggesting that the processes mediating recovery from sleep loss are partially driven by sex chromosome complement (Ehlen et al., 2013). Other studies which addressed the effects of genetic and phenotypic sex interactions in the case of sex differences in circadian responses to light (Kuljis et al., 2013) or in the control of diurnal rhythms of food intake (Chen et al., 2015) have concluded that both SCC and gonadal hormones are involved in sex differences in their observations. Considering this evidence, it is therefore reasonable to propose that sex differences in sleep architecture and homeostatic sleep responses originate from both sex-biasing factors.

### 1.2. Sex differences and gonadal hormone influences on cognition

Sex differences in respect of cognitive functions are among the most interesting and best studied areas of neuroscience dealing with sexual dimorphisms in the brain and behavior. In this section, we briefly review some learning and memory abilities known to show differences between the sexes and the potential involvement of gonadal steroid hormones in these behavioral differences.

Sex-related differences in spatial memory are one of the oldest and most widely reported paradigms of cognitive sex differences. Since the first reports in the 1970's suggesting that males performed better in tests of spatial abilities than females (Vandenberg and Kuse, 1978), numerous studies have consistently repeated these findings (Gagnon et al., 2018; Voyer et al., 2017). In spatial rotation ability, which is generally considered a form of spatial memory, males have also been shown to outperform women in several studies (Maeda and Yoon, 2013; Parsons et al., 2004). Neuroimaging studies that examined sex differences in respect of mental rotation have indicated that there is activity in different brain regions between the sexes (Hugdahl et al., 2006; Semrud-Clikeman et al., 2012). In men, the parietal cortex shows the most activation during mental rotation, while in women greater activation is seen in the right frontal regions during these tasks (Hugdahl et al., 2006). The unique brain activity in men and women has been interpreted as evidence of different cognitive strategies being used to resolve mental rotation problems (Hugdahl et al., 2006).

Some researchers, however, have challenged the validity of this male advantage by considering moderating factors that are part of the task process. There are studies suggesting that the mental rotation process is not the sole source of the sex difference in mental rotation tasks. Indeed, they believe that factors such as the alternative strategy used (Boone and Hegarty, 2017) or the processing speed of the participants (Debelak et al., 2014), as well as artifacts of the stimuli (Fisher et al., 2018) could also be sources of sex differences in these tasks. Therefore, to fully understand the specific nature of the reported male advantage in spatial abilities, one must apply tasks which challenge different moderating factors in spatial memory.

In spatial navigation, in which the participants are asked to rebuild a route through a map, virtual environment or real word space, males have shown higher accuracy and faster completion time (Brake and Lacasse, 2018; Coluccia et al., 2007; Woolley et al., 2010). It seems that the differences between men and women in navigation tasks are based

on different strategies regarding the use of landmarks (Boone et al., 2018). For example, when men and women were tested to navigate a virtual water maze, performances were dependent on the amount of information provided by landmarks (Rizk-Jackson et al., 2006). If landmarks are invisible or not in a fixed position, men significantly outperform women. Conversely, if the landmarks are visible and their positions are the same in training and testing, the differences in performances are eliminated (Rizk-Jackson et al., 2006). However, if women can perform the task as well as men when using landmarks, why are sex differences still evident when participants are free to use any cognitive strategy they choose? Stress may be one reason. It has been proposed that wayfinding in navigation tasks produce significantly higher levels of spatial anxiety in women and that this anxiety is elevated by versions of the task that tend to favour men (Lawton, 1994). Therefore, as stress affects cognition differently in the two sexes (Andreano and Cahill, 2009; Gabriel et al., 2011; Guenzel et al., 2014), according to Welvaart (Welvaart, 2017), performance differences may be an artefact of stress. Differences between the sexes in various spatial performances have also been extensively reported in animal studies (Brake and Lacasse, 2018; Saucier et al., 2008). A positive relationship of both navigation and rotation abilities with circulating testosterone levels has been found (Falter et al., 2006). Clear sex differences have not been found in these tasks at prepubertal ages (Leplow et al., 2003), reinforcing the idea that testosterone may play a role in successfully performing these tasks. In some other studies, however, both positive and negative relationships between testosterone and spatial ability have been reported (Kubranska et al., 2014; Silverman et al., 1999).

Verbal fluency and word recall are two categories of verbal memory in which women have been shown to outperform men in several studies (Barel and Tzischinsky, 2018; Sundermann et al., 2016). Women have also been shown to be better at other measures of episodic verbal memory such as verbal recognition and story recall (Grysmann, 2017; Herlitz and Rehnman, 2008). In contrast to the male advantage in spatial tasks, the involvement of gonadal hormones in the female advantage in verbal memory performance is not so clear. Although sex differences for verbal tasks have been reported to be consistent across the life span (Gale et al., 2007), some have demonstrated that sex differences in verbal fluency are more age dependent (Rodríguez-Aranda and Martinussen, 2006). Yonker et al. showed that when groups of men and women with the same estradiol levels were compared, women nonetheless outperformed men at verbal recall (Yonker et al., 2003). On the other hand, Rentz et al. underscored the significance of ovarian estradiol levels and reproductive aging in sex differences in verbal episodic memory (Rentz et al., 2017).

Sex-related differences have been demonstrated in episodic memory, which is related to the recall of life events. Several studies have reported that women's recall is more detailed and more accurate than men's (Grysmann, 2017; Herlitz and Rehnman, 2008; Bloise and Johnson, 2007; Grysmann and Hudson, 2013). Women's narratives are longer than men's and they recall more life events, recall their first event more quickly and the first items remembered are significantly earlier in life (Davis, 1999; Grysmann and Hudson, 2013). As these differences are evident in childhood (Davis, 1999; Grysmann and Hudson, 2013), they also do not seem to be related to sex hormones.

Consistent with the established sex differences in cognitive functions, a variety of neurobiological substrates underlying cognition have been shown to exhibit sex differences at various levels including in gross neuroanatomy, circuit properties, and molecular and cellular mechanisms. Many studies have demonstrated larger whole brain volumes and higher ratios of white to grey matter in men than women (Bourisly et al., 2017; Ruigrok et al., 2014). The volume of various brain regions implicated in learning and memory have, in particular, been shown to be significantly different between the sexes. Imaging studies report, for example, that relative to total brain size, the hippocampus, Broca's area, the caudate nucleus, dorsolateral prefrontal cortex, and anterior cingulate gyrus are larger in women than in men (Goldstein et al., 2001;

Lenroot and Giedd, 2010; Ruigrok et al., 2014). In contrast, men have larger relative volumes of the amygdala (Giedd et al., 1996; Lenroot and Giedd, 2010) and paracingulate gyrus (Clark et al., 2010).

One region with marked sexual dimorphism in structure and function is the hippocampus, the area most associated with learning and memory. In addition to the relative larger size in women (Lenroot and Giedd, 2010; Ruigrok et al., 2014), there is also evidence of sex differences in several neurotransmitter systems within the hippocampus, including the serotonergic, adrenergic, cholinergic, corticosterone, and benzodiazepine systems (Vries, 1990). For example, receptor affinity of glucocorticoids in male rats is twice that in females, a difference that is not related to the circulating sex hormones (Turner, 1985). Finally, differences between the sexes also exist in hippocampal long-term potentiation (LTP), a widely accepted cellular model of memory formation (Monfort et al., 2015; Qi et al., 2016; Yang et al., 2004). Although both spaced and continuous tetanic stimulation can induce hippocampal LTP in male rats, female hippocampi react only to continuous stimulation (Yang et al., 2004).

### 1.3. Sex differences in cognitive deficits induced by sleep deprivation

The evident sex differences in sleep architecture and homeostatic responses to sleep loss, as well as in cognitive functions and corresponding neurobiological substrates mentioned above, encouraged studies to test if there are also differences in the extent of the negative effects of sleep deprivation on learning and memory between male and female rats.

The results of a Morris water maze spatial performance test in male and female animals following 72 h of PSD using a multiple platform technique showed mild, insignificant impairment in spatial memory in male rats, while it significantly disrupted the memory of female animals (Hajali et al., 2012) (Fig. 1). Interestingly, another study consistently found that the impairing effects of SD on emotional memory retrieval can be more severe in female mice depending on the memory task evaluated (Fernandes-Santos et al., 2012). In this study, the effect of 6 h of total sleep deprivation on different emotional memory tasks in male and female mice was examined. Although SD caused the same degree of impairment in the fear conditioning context and the passive avoidance task in male and female mice, it disrupted the performance of the female mice significantly more than the males in the plus-maze discriminative avoidance task (Fernandes-Santos et al., 2012). There is a paucity of animal studies focusing on the potential differences in the severity of sleep deprivation induced cognitive impairments between the sexes. In this context, we were surprised to find such striking sex

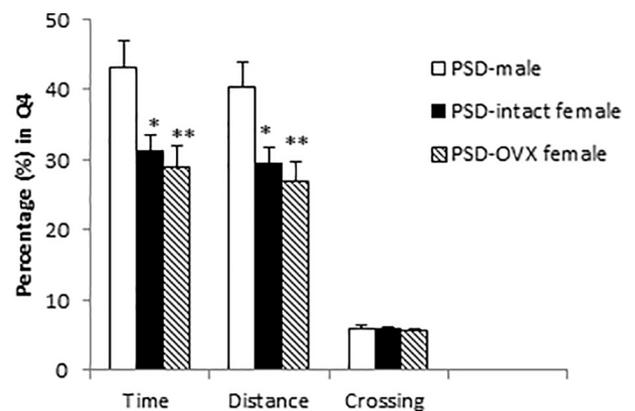


Fig. 1. Effects of 72 h paradoxical sleep deprivation (PSD) on spatial memory in male, intact female and ovariectomized (OVX) female rats. Spatial memory in the Morris water maze (MWM) test is defined as the time and distance spent in the target quadrant as well as number of crossings of this quadrant. \* $P < 0.05$  and \*\* $P < 0.01$  indicating difference from PSD-male group. Redrawn from Hajali et al. (2012).

differences in a most recent study which compared the impact of 6 h of SD on hippocampal dependent memories and kynurenic acid (KYNA), an endogenous astrocyte-derived neuroinhibitory molecule resulting from tryptophan metabolism, formation in male and female rats (Baratta et al., 2018b). The results revealed that while both male and female sleep-deprived rats were impaired in a recognition memory task (novel object recognition), only male animals showed impairment in a contextual memory paradigm (the passive avoidance task) and significant elevation of hippocampal KYNA levels (Baratta et al., 2018b). Regarding the impairing effects of KYNA on cognitive functions (Alexander et al., 2012), the observed elevation in brain KYNA after SD in male animals suggests that KYNA could serve as a key molecular link between sleep disturbances and cognitive deficits. This study implies a resilient advantage of female animals to acute sleep loss in the contextual memory task, but not the recognition memory task. (Baratta et al., 2018a). The small differences in the degree of susceptibility of the two sexes to the impairing effects of sleep loss on cognitive functions may be due to the different cognitive tasks evaluated as well as the different durations or models of sleep loss. The multiple platform technique, which involves the loss of muscle tone during REM sleep episodes, has been demonstrated to completely suppress REM sleep (shown by the electrophysiological recording of the sleep deprived animals). However, it was reported that this technique also slightly reduces NREM sleep, but does not lead to rebound sleep (Machado et al., 2004). It thus seems that this paradigm can predominantly produce PSD rather than elicit total sleep deprivation. PSD induced by the single flowerpot model, an early version of the platform method, was reported to be associated with increased stress axis activity (McDermott et al., 2003). Stress hormones can impair cognitive functions, so it may be difficult to distinguish between the effects of stress and loss of sleep. However, in more recent studies, the modified multiple platform model has been used, in which animals from the same cages are sleep deprived simultaneously and can move freely between the platforms. This avoids the possible isolation or immobilization stress related to the earlier flowerpot model. Plasma corticosterone levels have been shown not to be increased in animals with PSD induced by this technique (Hajali et al., 2012; Hajali et al., 2015a; Hajali et al., 2015b; Ravassard et al., 2009). Furthermore, administration of metyrapone, a glucocorticoid synthesis inhibitor, or surgical removal of the adrenal glands (with corticosterone replacement to non-stressed levels) in PSD rats induced by the same technique could not protect animals against the sleep loss-induced memory deficits (Ruskin et al., 2006; Tiba et al., 2008). These observations could diminish the possibility that stress contributed to the memory impairments seen in rats deprived of REM-sleep by the multiple platform technique. Despite these interesting findings, to date, no other animal study has addressed the potential differences in the severity of sleep deprivation induced cognitive impairments between the sexes.

The few available human studies concerning this issue also consistently suggest that sleep deficit may have a differential impact on cognitive functions in men and women. Most recently, Rångtjell et al. examined the impact of a single night of SD on objective and subjective working memory performance in healthy adult men and women (Rångtjell et al., 2018). They found that while both measures remained unaffected in men, sleep loss impaired objective working memory in women. Sleep loss, however, had no effect on subjective memory in women (Rångtjell et al., 2018). According to the results of the National Sleep Foundation's (NSF) 2005 Sleep in America poll, after < 7 h sleep, men generally function better than women during the day (Drake et al., 2005). In the case of shift work, women also seem to be more adversely affected by acute and chronic sleep insufficiency (Saksvik et al., 2011). The adverse effects of SD on alertness have been shown to be more profound in women than in men both in laboratory setting (Blatter et al., 2006; Vidafar et al., 2018) and in shift work settings (Axelsson et al., 2004). Increased injury risk among shift workers could be due to cognitive deficits resulting from sleep disruptions (Geiger-Brown et al.,

2012; Kling et al., 2010) and, in fact, women have been shown to have higher rates of work-related injuries than men on night shifts (Australia, 2012; Saksvik et al., 2011). This evidence again suggests that women are more vulnerable to cognitive deficits induced by sleep loss. However, other studies (Binks et al., 1999; Corsi-Cabrera et al., 2003) have suggested that certain aspects of cognition may be more affected by sleep loss in men than women. In one study by Binks et al., young women obtained better scores than men in an IQ test following 35 h of SD, despite men scoring higher than women in the normal sleep condition (Binks et al., 1999). However, there were no sex differences in any other measures, including cognitive flexibility, sustained attention and word fluency (Binks et al., 1999). Another study reported that 38 h of SD in young men had more severe effects on sustained attention (as displayed by slower response times) than in women (Corsi-Cabrera et al., 2003).

The reported discrepancies in the available data can be attributed to the different periods of sleep loss, cognitive tasks, experimental subjects and variation in how the investigators interpreted their findings. Hence, given the limited number of available studies, it is difficult at present to claim with certainty which sex is more vulnerable to the detrimental effects of sleep loss on cognitive performance. Nevertheless, as mentioned in the previous sections, due to the greater and quicker accumulation of sleep pressure in women (Armitage and Hoffmann, 2001; Mong et al., 2011), it still seems reasonable to assume that the impacts of sleep loss for women in general are more detrimental to their somatic and cognitive health than they are for men. Consistently, recent studies have reported that poor sleep puts women at a greater risk for developing cardiovascular and metabolic disorders (Cappuccio et al., 2007; Grandner et al., 2018; Miller et al., 2009; Simpson et al., 2010).

As sleep quality changes with age in both sexes, discrepancies in the susceptibility of men and women to the deleterious effects of sleep loss on cognitive abilities may also emerge when assessing cognition in elderly individuals. It seems that aging has a greater impact on sleep, and thereby on cognition, in women than in men, but very few studies on this subject are available. In a recent nationwide survey of subjects over 65 years old in Taiwan in, women showed greater impairment in global functioning as measured by the Mini Mental Status Test than men, but biological sex had no significant effect on the negative impacts of sleep disturbances on cognition (Chiu et al., 2016). In men, habitual snoring, difficulty breathing during sleep, and prolonged sleep duration correlated significantly with cognitive impairment, whereas in women, only prolonged sleep duration was associated with cognitive scores (Chiu et al., 2016). More studies are needed to determine whether aging can influence the relationship between sleep and cognition in men and women.

#### 1.4. Gonadal hormone influences on cognitive deficits induced by sleep deprivation

While many reported sex differences in sleep homeostatic responses are thought to be mediated by gonadal steroids (as mentioned in the previous sections), it is tempting to assume that these hormones may also affect the sensitivity of male and female subjects in respect of the impairing effects of sleep loss on cognitive abilities. However, this issue has not yet been sufficiently addressed. There have been studies comparing gonadectomized male (GDX) and female (OVX) rats with their gonadally intact counterparts to explore the possible involvement of male and female sex hormones in sleep deprivation induced cognitive and synaptic deficits. In one study, sleep deprived OVX female rats had the most impaired learning ability in the Morris water maze task (Fig. 2) (Hajali et al., 2012). Depletion of ovarian hormones made the female rats more predisposed to the deleterious effects of SD on cognitive function (Hajali et al., 2012). A study examining the protective role of ovarian hormones against the detrimental effects of SD on spatial memory consolidation also reported an effect on sleep deprived OVX female rats (Esmailpour et al., 2015). In this study, gonadally

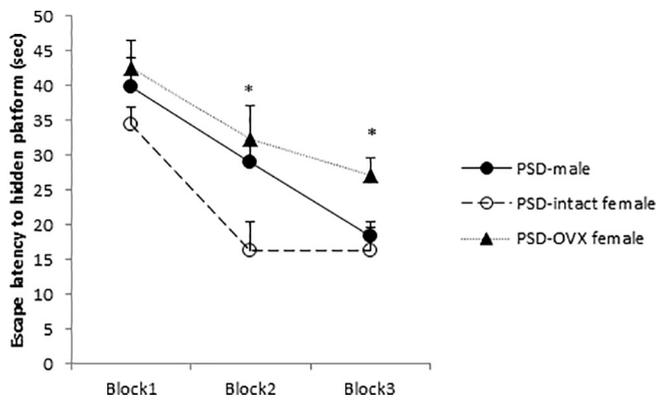


Fig. 2. Effects of 72 h paradoxical sleep deprivation (PSD) on spatial learning in Morris water maze (MWM) test in male, intact female and ovariectomized (OVX) female rats. Each block represents the mean latency of four consecutive trials to find the hidden platform. \* $P < 0.05$  indicating the difference from the PSD-intact female group. Redrawn from Hajali et al. (2012).

intact and OVX female rats were submitted to 72 h of SD using a multiplatform chamber. SD impaired spatial performance in a water maze, but only in the OVX animals (Esmailpour et al., 2015). In the previously mentioned human study investigating sex differences in respect of the effect of SD on subjective and objective alertness, women in the follicular phase of the ovarian cycle demonstrated the poorest level of performance after 30 h of wakefulness in a laboratory setting (Vidafar et al., 2018). In the luteal phase, when both estrogen and progesterone are high, however, they were relatively protected from alertness deficits, performing similarly to, or better than, both women in the follicular-phase and men (Vidafar et al., 2018).

Such observations can partly be explained by the findings of previous studies showing that estradiol reduces the homeostatic drive for REM sleep after SD (Hadjimarkou et al., 2008; Schwartz and Mong, 2011; Schwartz and Mong, 2013). Thus, since REM sleep is mainly blocked in the multiplatform technique (Machado et al., 2004), in the absence of estradiol, the need for REM sleep is accumulated more efficiently in REM sleep-deprived OVX animals. On the other hand, REM sleep is the most critical type of sleep in relation to sleep-dependent memory processing. These findings suggest that physiological levels of ovarian hormones may be essential for maintaining cognitive abilities in sleep deprived subjects. Their protective effects have also been reported against a variety of neural insults, brain injuries, and neurodegenerative diseases (Pike et al., 2009; Siddiqui et al., 2016).

In another study, authors explored the potential roles of sex hormones as a predictor of susceptibility or resiliency in emotional processing tasks following one night of sleep restriction. Sleep restriction decreased testosterone levels upon awakening in men, but had no effects on sex hormone concentrations in women (Lustig et al., 2018). Carter et al. previously reported a reduction of testosterone in men and progesterone, but not estradiol, in women in a sample of men and women deprived of sleep for one night (Carter et al., 2012). Thus, it seems that there is a dose-response relationship with the degree of sleep disturbances and alteration of hormone concentrations in women. The previously mentioned study (Lustig et al., 2018), demonstrated that women with higher progesterone and men with lower testosterone levels were more vulnerable to the negative effects of sleep restriction on emotion processing tasks. This study again highlighted the role of sex hormones in cognitive vulnerability to sleep loss.

A study to test whether reproductive status in sleep deprived rats affects memory formation at the cellular level measured hippocampal LTP in gonadally intact and OVX female SD rats (Hajali et al., 2015b). However, the study found no significant effect of reproductive status or any interaction between treatment and reproductive status in LTP formation (Fig. 3A). In the other words, LTP was significantly, but

similarly impaired in both gonadally intact and OVX female animals following sleep deprivation (Hajali et al., 2015b). These data, unlike those reported earlier (Esmailpour et al., 2015; Hajali et al., 2012), suggest that ovarian hormones may not exert any protective role against the impairing effects of sleep loss on cellular correlates of memory formation. These discrepancies may partly be due to the different duration of SD (that is 72 h in first and 48 h in the second experiment) and also to the different statistical analyses used. To the best of our knowledge, no other study has yet addressed the impact of ovarian hormone depletion on the association between sleep and memory formation in animals.

The potential influence of female sex hormones on sleep and cognition can be extrapolated from sleep quality and cognitive abilities in postmenopausal women. However, findings from studies into the effects of ovarian hormones on sleep and cognition in postmenopausal women are few and inconsistent. A study by Saletu reported that hormone replacement therapy for two months has a beneficial effect on subjective and objective sleep quality, as well as on sustained attention and information processing speed in postmenopausal women (Saletu, 2003). In contrast, two other studies found no such benefit from hormone therapy on cognitive functions in postmenopausal women (58–72 years old) following SD (Alhola et al., 2005; Karakorpi et al., 2006). The studies reporting negative findings used small sample sizes and assessed a limited set of cognitive domains. While sleep is critical for sustained attention, which was measured in these studies, other performances including spatial memory, decision making, task switching and response inhibition are also influenced by sleep.

If ovarian hormones benefit sleep and play a protective role against the detrimental effects of sleep disturbances on cognition, the loss of these hormones at menopause would be expected to accelerate cognitive decline, first by increasing sleep disturbances, and second by intensifying their impact on cognitive functions. As mentioned in previous sections, menopausal transition is associated with a dramatic increase in sleep disturbances. In addition, increasing evidence suggests that sleep dysfunction may contribute to age-related cognitive decline and potentially progression to Alzheimer's disease (Mander et al., 2016; Winer and Mander, 2018). Further research, however, is needed to clarify whether female sex hormones can regulate the impact of sleep loss on cognition.

Unlike the relatively well-established effects of gonadal steroids on homeostatic responses to sleep loss in women, the influence of sex hormones, mainly testosterone, in men is not well defined. Androgens have been demonstrated to affect cognitive functions and their neural substrate within the hippocampus (Skucas et al., 2013; Wagner et al., 2018). In addition, male sex hormones have been reported to have a protective role against experimental and pathological neural injuries (Gurer et al., 2015; Huo et al., 2016). Regarding cognitive decline in elderly subjects, testosterone replacement has been shown to exert a positive impact on cognitive deficits in elderly men and also in men with Alzheimer's disease (Holland et al., 2011; Lu et al., 2006). However, so far, very limited data exists on the extent of the deleterious effects of poor sleep in gonadal hormone-depleted male subjects (e.g., aging men or gonadectomized animal models). In the above mentioned human study by Lustig et al., the authors demonstrated that men with lower levels of testosterone were more vulnerable to the negative effects of one night of sleep restriction in respect of emotional processing of both faces and images (Lustig et al., 2018). Another study compared intact and GDX male rats to explore the possible protective effect of endogenous male sex hormones against 48 h sleep deprivation-induced cognitive and synaptic impairments (Hajali et al., 2015a). This study also did not establish any significant effect of reproductive status or interaction between treatment and reproductive status on cognitive functions or their neural correlates (Fig. 3B). Indeed, like ovarian hormones in previous study, male gonadal hormones showed no protective role against the impairing effects of SD on behavioral and synaptic plasticity (Hajali et al., 2015a).

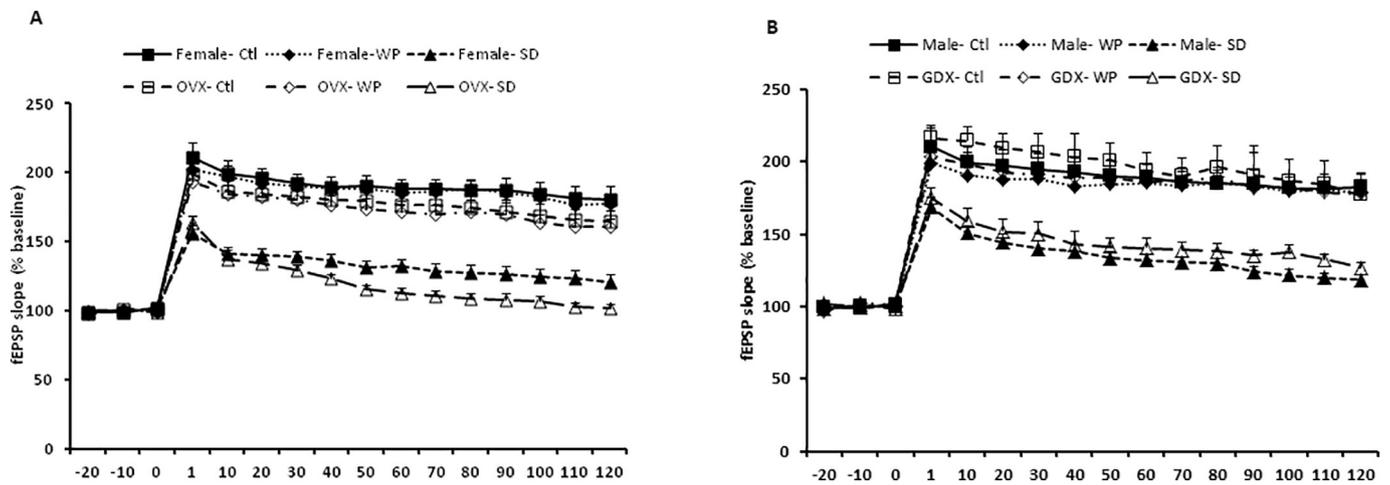


Fig. 3. Effect of 48 h sleep deprivation (SD) on the induction and maintenance of long term potentiation (LTP) over a period of 120 min in the hippocampal CA1 area of gonadally intact and gonadectomized female (OVX)(A) and male (GDX) (B) rats. The magnitude of LTP is expressed as relative change (%) in the slope of fEPSP after high frequency stimulation (HFS) with respect to the average of responses during a 20 min period of baseline recording. Reproductive status and treatment independently impaired the LTP maintenance. WP: wide platform. Redrawn from Hajali et al., 2015a, 2015b.

There may be an evolutionary reason for the lack of a protective effect of gonadal hormones found in our studies; however, experiments using different cognitive tasks, protocols and periods of SD or looking at different species may provide evidence of this effect. As we selectively deprived animals of REM sleep in our studies, it should also be mentioned that the protective potentials of these hormones could be more pronounced after total sleep deprivation.

In addition to the gonadal-derived sex steroids, there has been increasing evidence that some brain regions, especially the hippocampus, also synthesize their own steroids (neurosteroids). It has been shown that sex steroids remain within the hippocampus long after gonadectomy and adrenalectomy and that these brain-derived steroids are neuroprotective and critical for synaptic plasticity (Di Mauro et al., 2015; Hojo and Kawato, 2018). Therefore, it cannot be ruled out that the hippocampal neurosteroids may have masked the protective impacts of gonadal steroids in our observations.

Finally, Cahill (Cahill, 2006) highlighted a widespread misconception about sex differences in neuroscience, namely that “all sex differences, once established, can be completely explained by the action of sex hormones, typically oestrogen”. Sex hormones are crucial for many sex differences in the brain and behavior but they cannot account for all sex differences in experimental and clinical observations. Indeed, numerous studies report that sex chromosomes, rather than gonadal hormones, mediate sex differences in a variety of behavioral responses (Bonthuis et al., 2012; Cox and Rissman, 2011; Liu et al., 2010). As discussed in the previous sections, using the FCG mouse model in future studies could dissociate the potential roles of gonadal hormones from those of sex chromosomes in the differential cognitive vulnerability of male and female subjects to sleep loss.

## 2. Conclusions

The critical role of sleep in memory processing has been well documented in both human and animal studies. The importance of sex differences and gonadal steroids in sleep and homeostatic responses to sleep loss is gaining attention due to the increasing knowledge about sleep differences between males and females. However, their precise influence on the susceptibility to the deleterious effects of sleep loss on cognitive functions remains to be fully elucidated. Conducting studies with different periods of SD and different cognitive tasks, as well as using subcutaneous sex steroid implants in gonadectomized male and female animals, can help to increase our knowledge in this area. Finding out more about male and female responses to the detrimental

effects of insufficient sleep on cognition, and how neuroendocrine mediators influence cognitive impairments induced by SD could help to develop more effective therapies tailored to each sex.

## Disclosure statement

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