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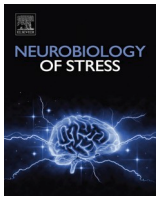

The stress of losing sleep: Sex-specific neurobiological outcomes

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ABSTRACT

Sleep is a vital and evolutionarily conserved process, critical to daily functioning and homeostatic balance. Losing sleep is inherently stressful and leads to numerous detrimental physiological outcomes. Despite sleep disturbances affecting everyone, women and female rodents are often excluded or underrepresented in clinical and pre-clinical studies. Advancing our understanding of the role of biological sex in the responses to sleep loss stands to greatly improve our ability to understand and treat health consequences of insufficient sleep. As such, this review discusses sex differences in response to sleep deprivation, with a focus on the sympathetic nervous system stress response and activation of the hypothalamic-pituitary-adrenal (HPA) axis. We review sex differences in several stress-related consequences of sleep loss, including inflammation, learning and memory deficits, and mood related changes. Focusing on women's health, we discuss the effects of sleep deprivation during the peripartum period. In closing, we present neurobiological mechanisms, including the contribution of sex hormones, orexins, circadian timing systems, and astrocytic neuromodulation, that may underlie potential sex differences in sleep deprivation responses.

1. Introduction

Sleep disturbances are increasingly common amongst the general population, affecting nearly 50–70 million US adults, and encompass a variety of consequences that may worsen symptom severity of numerous disease states. The plentiful consequences of sleep disruption often include exacerbations of the body's stress response. Both poor sleep and elevated stress can exaggerate the incidence of diseases or worsen disease symptoms but are also frequently listed as symptoms of the same conditions. Yet, while a wide swath of work has detailed the role of stress in the etiology of disease, less work has focused on the role of sleep in mediating the transition to disease state. Additionally, evidence from animal studies strongly suggests a bidirectional relationship between stress and sleep, such that stress exposure can impact sleep and sleep, particularly sleep loss, can impact stress responsivity (Lo Martire et al., 2020; Meerlo et al., 2008; Nollet et al., 2020; Pawlyk et al., 2008; Sanford et al., 2014). Nonetheless, the impact of stress exposure on sleep has been much more readily studied than the effects of sleep loss on stress. As sleep loss and chronic stress produce many similar detrimental outcomes, understanding the neurobiological underpinnings of these relationships is highly significant and warrants special consideration. Importantly, the consideration of sleep loss as a primary stressor is critical.

Investigating both men and women is critical when considering the effects of sleep loss. Studies often are underpowered to evaluate the impact of sex and when differences do appear, investigations fail to explore the changes that appear between these groups comprehensively. Women typically complain more frequently of sleep disturbances than men, and specific life events like pregnancy and menopause are associated with increased sleep disturbances and stress-related conditions. As sleep is an evolutionarily conserved phenomenon and has been readily studied across a variety of animal species including sheep, cats, dogs, non-human primates, and rodents, animal models are valuable tools for research. These models are further invaluable as they have more recently begun to provide clarity on the underlying biological framework for sex differences in response to physiological challenges such as sleep loss and stress responsivity. Preclinical models provide opportunities for deeper investigation into biological mechanisms and processes than what is possible in humans, including the effects of sleep deprivation (SleepDep). The current review seeks to examine what is currently known about the sex-specific, stress-related consequences of SleepDep in humans and rodents. Compared to SleepDep studies in other model species, rodent SleepDep studies so far provide the most thorough investigation into both sexes and will therefore comprise the animal studies included in this review.

Our review will first provide a background on the function and

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importance of sleep, noting its restorative properties, then advance to discussing the history and progress of SleepDep techniques. We will present an overview of the stress responses followed by a deeper diver into sex-specific reactions to SleepDep observed in human and rodent studies. Finally, we will introduce potential mechanisms that may be critical for the sex-specific stress responses to SleepDep.

1.1. What is sleep?

Sleep is an essential homeostatic process that remains highly conserved across species. It is well accepted that adequate sleep is vital, yet the exact purpose of sleep remains contested, and several hypotheses postulate its purpose. Daily sleep allows for greater homeostatic control by increasing glymphatic clearance of waste metabolites that accumulate during wakefulness (Plog and Nedergaard, 2018; Xie et al., 2013). Theories also suppose that sleep is essential for memory consolidation, as declarative and non-declarative memories are enhanced after periods of sleep during which synaptic connections strengthen following potentiation during wakefulness, the so-called "synaptic homeostasis hypothesis" (Tononi and Cirelli, 2014). Further, as wakefulness is an energetic challenge to the brain, sleep may act to conserve and replenish energy stores for the brain and allow for repair and restoration processes (Benington and Heller, 1995). It is more than likely, however, that sleep serves many essential functions.

Sleep itself occurs in a cyclic process divided into non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep and can be recorded in humans and rodents by various methods. In humans, sleep stages are typically differentiated by combining electroencephalography (EEG), measured cerebral electrical activity, with electromyography (EMG), muscle electrical activity, and electrooculogram (EOG), eye movement. In humans, non-invasive head caps with EEG electrodes can acquire sleep data with minimal intrusion, typically during an overnight clinical visit. In small animal subjects such as rodents, EEG and EMG electrodes are surgically implanted, such that EEG electrodes are secured to the skull and EMG wires are placed into the cervical neck muscle. The electrodes are either tethered to a recording system or attached to a radio telemetry device implanted in the abdominal cavity. Telemetry recordings allow for untethered locomotion within the animal's home cage. The collected polysomnography data can then be classified into distinct vigilance stages including wake, NREM sleep and REM sleep.

In humans, initiation of sleep typically occurs with a transition from wake to NREM sleep at the beginning of a sleep cycle, and this transition results in a characteristic change in the EEG from high frequency, low amplitude during the waking state to a high amplitude, low-frequency EEG in the NREM state. NREM sleep consists of three successively deeper stages of sleep. Stage 1 NREM sleep is a transitional sleep state wherein the body transforms by initially slowing down heartbeat, eye movements, and cortical oscillations. During Stage 2 NREM sleep, body temperature reduces, and unique oscillatory features including sleep spindles and K complexes, important for synaptic plasticity, procedural and declarative memory consolidation, and maintaining sleep, occur (Antony et al., 2019; Gandhi and Emmady, 2022). Stage 3 NREM sleep is considered the deepest stage of sleep and is often called slow wave sleep for its characteristic high amplitude, low frequency delta waves. Stage 3 NREM sleep is important for maintaining bone, muscle, and immune system function and supports physical recovery as the brain uses significantly less energy during this slower oscillatory state (Huang et al., 2018; Léger et al., 2018; Xu et al., 2020).

From NREM sleep, brain oscillations transition to lower amplitude, higher frequency EEG and muscle atonia, which defines REM sleep (Carskadon and Dement, 2011). The abolished muscle tone, low-frequency EMG signals, and EEG rhythms that appear strikingly similar to the waking state lend REM sleep to be termed a paradoxical state (Carskadon and Dement, 2011). REM sleep is critical for brain development and cognitive functions as REM sleep is highest in early life and infancy and increases after episodes of learning (Crick and Mitchison, 1983; Peever and Fuller, 2017; Rasch and Born, 2013; Smith and Lapp, 1991). REM sleep also contributes to emotional processing as limbic structures including the hippocampus and amygdala are activated during this sleep state. As the sleep period progresses in humans, REM sleep typically occurs in more prolonged bouts with each sleep cycle; thereby, the recommended 7–8 h of nightly sleep in humans promotes sufficient REM sleep duration which, along with NREM sleep, contributes to restorative sleep quality.

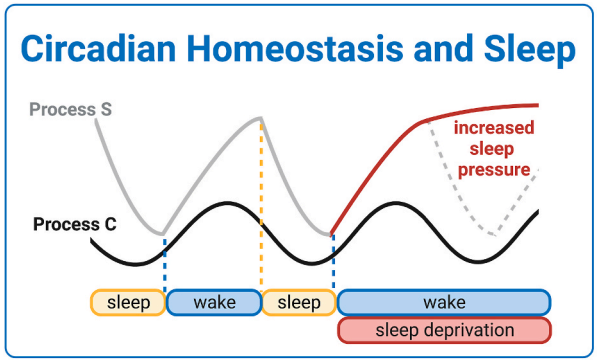

Fig. 1. Schematic representation of the relationship between circadian homeostasis and sleep. Process C (circadian rhythmicity) and Process S (homeostatic sleep drive) keep sleep regular and appropriately timed. Process C fluctuates throughout the day while Process S builds with increased wakefulness and decreases with sleep. The difference between the two processes dictates sleep pressure, which is increased during sleep deprivation.

Further physiological differences exist between NREM and REM sleep. Notably, sympathetic activity, critical to directing the body's homeostatic responses, is higher in REM sleep than during wakefulness but lower during NREM sleep. Changes in body temperature and brain temperature, processes tightly controlled by the sympathetic nervous system, occur during NREM and REM sleep such that body temperature decreases during NREM sleep and brain temperature increases during REM sleep (Somers et al., 1993). Further, changes in cardiovascular activity, cerebral blood flow, and respiration occur between NREM and REM sleep. Reductions in blood pressure that occur with nightly restorative NREM slow wave sleep have been implicated as protective against heart disease (Huang et al., 2018). These distinct features of each sleep stage support the notion that they serve separate functions. Irregular cycling or absence of sleep stages are often associated with sleep disorders (Zepelin and Rechtschaffen, 1974), and healthy, restorative sleep critically encompasses both NREM and REM sleep stages, thus making it imperative to evaluate both classifications when studying sleep.

NREM and REM sleep stages are conserved across species, despite interspecies differences in accumulation of restorative sleep (Tobler, 1995). Humans are monophasic, and typically diurnal sleepers, thereby predominantly sleeping in a single, prolonged period that occurs at night (Carskadon and Dement, 2011). Largely due to evolutionary reasons, rodents are nocturnally active, yet polyphasic sleepers, readily transitioning from wakefulness to sleep multiple times during a 24-h period (Van Twyver, 1969). In both humans and rodents, vigilance cycles are mediated by circadian and homeostatic mechanisms (Sanchez et al., 2022). Due to the conserved nature of these mechanisms, rodent models remain critical and advantageous for investigating sleep preclinically.

Circadian and homeostatic mechanisms that regulate sleep-wake rhythms are explained in part by the two-process model that postulates that the interplay between sleep drive, process S, and circadian rhythmicity, process C, keeps sleep regular and appropriately timed (Borbély, 1982). Process S is the homeostatic sleep pressure that builds with increased wakefulness and decreases with sleep. In contrast, process C is the circadian wake drive which promotes alertness and

fluctuates throughout the day. While the contributors to process S and process C may differ amongst species, the greatest differences between process S and process C dictate sleep initiation across species (Edgar et al., 1993) (Fig. 1).

1.2. What generates and maintains sleep?

Distinct neural circuits and neuromodulators also work to control wakefulness and sleep. In the anterior hypothalamus, the suprachiasmatic nucleus is considered the 'master clock' of the body. The suprachiasmatic nucleus does not function directly to initiate sleep but instead serves as a master pacemaker in the body that regulates the appropriate timing of sleep and wakefulness through the rhythmic expression of clock genes such as *Per*, *Cry*, and *BMAL1*. The suprachiasmatic nucleus receives direct input from the retinas through the retinohypothalamic tract, which entrains 24 h circadian rhythms through melanopsin produced by retinal ganglion cells (Berson, 2003; Hendrickson et al., 1972; Moore, 1973; Moore and Eichler, 1972; Moore and Klein, 1974). In an absence of light, the suprachiasmatic nucleus also regulates the production of melatonin from the pineal gland, a hormone that modulates the biological clock and whose secretion at night promotes sleep initiation in humans.

Early studies investigating sleep initiation found that sleep can be promoted and maintained by neurons in the preoptic area, a brain region also located in the anterior hypothalamus (McGinty and Sterman, 1968; Szymusiak and McGinty, 1986). Specifically, GABAergic inhibitory neurons in the ventrolateral and median preoptic areas are essential for NREM sleep while neuromodulators such as adenosine, prostaglandin D2, and cytokines help mediate the promotion of this sleep state (Krueger et al., 2011; Scammell et al., 2017). Excitatory cholinergic and glutamatergic neurons in the brainstem, respectively, contribute to REM sleep promotion and produce the characteristic muscle atonia (Boissard et al., 2002; Boucetta et al., 2014; Cox et al., 2016; Tsunematsu, 2021). Inhibitory GABAergic neurons in the lateral and preoptic areas of the hypothalamus, the medulla, and the pons can also promote REM sleep (Park and Weber, 2020). Interestingly, many sleep-promoting centers contain reciprocal projections with arousal systems such as the reticular formation, cholinergic basal forebrain, serotonergic dorsal raphe, noradrenergic locus coeruleus, histaminergic posterior hypothalamic tuberomammillary nucleus, and orexinergic lateral hypothalamus (Aston-Jones and Bloom, 1981; Chou et al., 2002; Hsieh et al., 2011; Jouvet, 1972; Kroeger et al., 2018; Lu et al., 2002; Sherin et al., 1998; Suntsova et al., 2002; Suntsova and Dergacheva, 2003; Uschakov et al., 2007; Yoshikawa et al., 2021). These neuronal populations' synchronized excitation or inhibition work to induce the appropriate vigilance states.

1.3. Introduction into sleep disruption and deprivation methods

Sleep disruptions occur through various mechanisms in humans, including lifestyle requirements (shiftwork, military enlistments, caring for a child or elder), life stressors (disease, trauma, financial insecurity), or at times even personal choices like staying up late. Nevertheless, the problems that arise from poor sleep do not stem merely from getting insufficient sleep. Reductions in sleep quality, fragmented sleep, frequent awakenings, or the mistiming of sleep can influence the overall value of daily sleep. In a preclinical laboratory setting, a common approach to study the impact of sleep disruption is through SleepDep, which can occur through various methods. In humans, SleepDep is accomplished through an overnight stay in a sleep laboratory. Commonly, the constant routine procedure keeps subjects awake in a stationary position in solitary room devoid of light and temperature changes with meals dispersed evenly over the duration of the protocol (Goel et al., 2013; Klerman and Bianchi, 2014). Tools such as environmental noise, ambulation, or activities to pass time such as television and books can keep people awake in these studies.

To keep animals continuously aroused, early methods of SleepDep involved constantly rotating treadmills or running wheels to keep the animals moving and, therefore, continuously awake (Borbely and Neuhaus, 1979). The "disk-over-water" apparatus was adapted to suspend one experimental and one yoked control rodent on a rotating platform over shallow water (Bergmann et al., 1989; Rechtschaffen and Bergmann, 1995; Rechtschaffen et al., 1983). When the experimental animal enters sleep, the platform rotates, forcing the animals to move to avoid falling into the water. Sleep is decreased in the experimental animal by roughly 90% and in yoked control animals by 30% (Rechtschaffen et al., 1983). SleepDep methods have also used pendulum motion, reticular formation stimulation, orbital shakers, rolling balls in tilted cages, environmental noise, or air puffs to keep animals awake (Datta et al., 2004; Gross et al., 2015; Grossman et al., 2000; Kovalzon and Tsibulsky, 1984; Mavanji et al., 2013; Shinomiya et al., 2003; Sinton et al., 2009; Van Hulzen and Coenen, 1980; Zhu et al., 2012). Also, alternating platforms placed inside a water tank were designed to repeatedly submerge and emerge from the water and deprive animals of sleep (Piérard et al., 2007). Taken together, while these experimental approaches have effectively reduced and disrupted sleep in small animals, the methods have also introduced stressful confounds, such as cold water temperature and forced locomotion that can cause excessive fatigue and prolonged stress for the animals. These experimental confounds may misconstrue how the conclusions of the experiment relate directly to sleep rather than the neurobiological underpinnings of stress and should be carefully considered as limitations of experimental design (Roman et al., 2006).

To starkly reduce the stress response, the technique termed gentle handing was introduced which effectively reduces 90–95% of NREM sleep and eliminates REM sleep. All while keeping the rodent in their home cage, animals are passively exposed to external stimuli (mild noise, cage tapping, gentle shaking of the cage, contact with a brush or Q-tip, introduction of novel objects or nesting material) to encourage spontaneous exploration and movement about the cage (Baratta et al., 2018; Endo et al., 1997; Franken et al., 1991; Oonk et al., 2016; Tobler et al., 1997; Toppila et al., 1997; van der Borght et al., 2006). As this method is quite labor intensive on the part of the investigator, recent advances have been made to automate SleepDep chambers. Automated treadmills, rotating drums, and activity wheels have been developed, but may also induce excessive locomotion in the animals (Christie et al., 2008; Leenaars et al., 2011). As such, chambers with a mechanical arm that sweeps the bottom of the cage were developed to force the animal to awaken and move only when it is nudged. Some of these chambers sweep the arm on programmed schedules, while others utilize live feedback from acquired EEG to sweep the arm only when specific sleep stages are detected. Chambers such as these have been successful in effectively reducing NREM and eliminating REM sleep with minimal locomotion and induced stress on the animals (Dumaine and Ashley, 2015; Fenzl et al., 2007; Mccarthy et al., 2017; Nair et al., 2011; Ramesh et al., 2009).

It is also possible to specifically deprive animals of only REM sleep, as opposed to total SleepDep. The first such method developed was the 'flowerpot method,' which placed rats on inverted flowerpots raised above the water. At the onset of REM sleep, when all muscle tone is lost, the sleep deprived animal loses balance and falls into the water, with the control animal resting on larger platforms that allow for sufficient balance (Cohen and Dement, 1965; JOUVET et al., 1964). More recently, investigators have adapted the flowerpot method to reduce immobilization and social isolation stress (Kovalzon and Tsibulsky, 1984; Patchev et al., 1991). First, the 'multiple platform method' added additional platforms into the experimental chamber to allow locomotion during wakefulness, while the 'modified multiple platform method' deprived multiple animals of sleep in one chamber to allow for social interaction (Allard et al., 2007; Hajali et al., 2012; Machado et al., 2004; Nunes Júnior et al., 1994; Suchecki and Tufik, 2000; van Hulzen and Coenen, 1981). Control animals for the multiple platform methods are typically

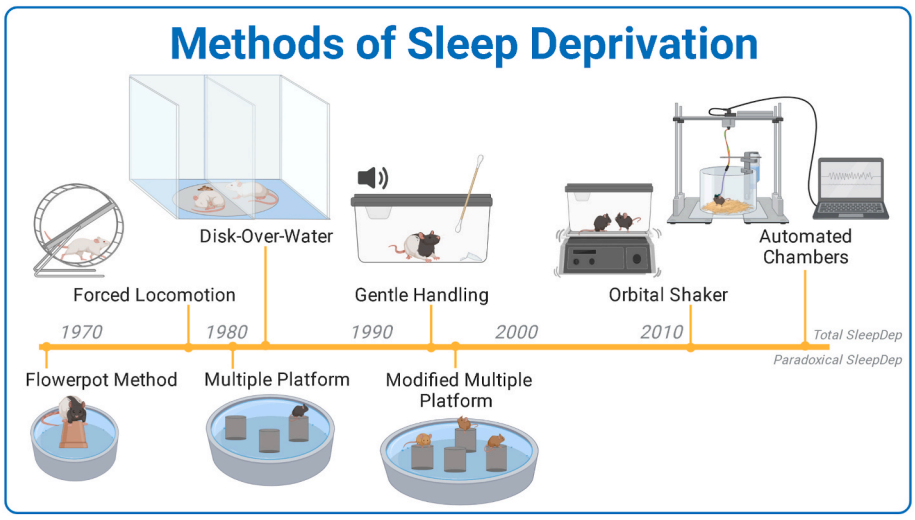

Fig. 2. Chronological timeline of experimental sleep deprivation (SleepDep) methods. Across time, methods of SleepDep have made strides to reduce stress and decrease requirements for experimenter intervention. The methods visualized above the timeline represent methods of total SleepDep while the methods visualized below the timeline represent methods of paradoxical SleepDep.

kept in the home cage (Alzoubi et al., 2012). As these techniques can eliminate REM sleep but typically reduce slow wave sleep by up to 30% (Machado et al., 2004, 2006), the approaches are frequently used when experimenters want to fragment sleep but not reduce sleep entirely and are called paradoxical SleepDep due to the stark impacts on REM sleep. In addition, REM sleep can also be deprived by monitoring the EEG and waking the animals when a transition from NREM sleep to REM sleep is detected, either manually or through automated approaches (Fenzl et al., 2007).

Recent advancements have also been made to manipulate sleep-wake neural circuitry and induce SleepDep opto- or chemo-genetically. This is accomplished by targeting specific receptors to either increase the activity of wake-promoting centers or decrease the activity of sleep-promoting centers. For example, stimulation of neurons in the parabrachial nucleus or the supramammillary nucleus (wake-promoting centers) can extend arousal, while silencing neurons in the ventrolateral preoptic nucleus or basal forebrain (sleep-promoting centers) has been shown to reduce sleep (Anaclet et al., 2015; Chung et al., 2017; Pedersen et al., 2017; Venner et al., 2016). Importantly, however, both sleep and wake are controlled by multiple brain regions that work together in tandem, so selective manipulation of just one brain region can fail to eliminate total sleep (Bringmann, 2019). Conversely, techniques such as these uniquely allow for precise temporal and spatial resolution that can elucidate the function of specific sleep stages, neuronal populations, or brain structures depending on the chosen targets (Frazer et al., 2021; Pastrana, 2011). Critically, in the context of this review, studies that implement methods such as these often show no activation of a stress response, and thus provide a method to investigate the effects of sleep loss without stress as a confounding variable (Frazer et al., 2021; Rolls et al., 2011).

Overall, many methods have been developed to effectively reduce, disrupt, or fragment sleep in rodents. Importantly, the history of SleepDep method development highlights the methodological advancements that have placed critical attention to reducing stress and minimizing potential confounds in experimental design (Fig. 2). A comprehensive list of SleepDep methods is provided in Table 1.

1.4. The stress response

Stress is an adaptive mechanism critical for preparing the body to handle perceived or expected internal or external challenges, i.e., stressors. The stress response can become maladaptive if inappropriately activated, or its activation is sustained, repeated, or particularly strong. The classic general adaption syndrome theory divides the stress response into three stages: alarm reaction, resistance, and exhaustion (SELYE, 1950). The body will continue to respond to a stressor if it persists, but this response is unsustainable and will lead to exhaustion, which is when stress typically becomes most detrimental. The stress response, including the stress-induced effects of SleepDep, includes two major components: the autonomic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis. Temporally, the autonomic nervous system triggers the sympathetic nervous system first which subsequently activates the HPA axis stress response. The HPA axis, an endocrine system, induces the release of epinephrine and norepinephrine from the adrenal medulla. These catecholamines act as both neurotransmitters and hormones to promptly activate α- and β-adrenergic receptors throughout the entire body. Contraction of vascular smooth muscles and cardiac tissue promoted by the sympathetic nervous system stimulation causes vasoconstriction, increased heart rate and blood pressure, bronchodilation, and reduced intestinal motility (Gordan et al., 2015). The sympathetic stress response can increase glucose levels and oxygen consumption and induce lipolysis and thermogenesis (Chu et al., 2022). Behaviorally, the sympathetic response can also increase arousal, alertness, cognition, and analgesia (Chu et al., 2022).

The HPA axis is activated by various physiological responses to stressors. In humans, experimental stressors often include a CRH or ACTH challenge or the psychosocial Trier Social Stress Test. In rodents, techniques such as social isolation, fear conditioning, restraint stress, chronic unpredictable mild stress, or social defeat stress are often used to elicit a stress response (Patchev and Patchev, 2006). Exposure to such stressors frequently results in altered sleep (Bush et al., 2022; Meerlo et al., 1997; Radwan et al., 2021; Yu et al., 2022). The body responds directly to stress, however, via the HPA axis with the release of corticotropin-releasing hormone from the paraventricular nucleus of the hypothalamus. Corticotropin-releasing hormone (CRH) stimulates the pituitary gland to release adrenocorticotropic hormone (ACTH) which, subsequently, triggers the adrenal glands to secrete glucocorticoids, such as cortisol in humans and corticosterone in rodents. As these glucocorticoids are the major effectors of the HPA axis, measurements of cortisol or corticosterone, typically in peripheral samples such as saliva or plasma, are most frequently used as biomarkers of HPA axis activation and the stress response (Bozovic et al., 2013; Hellhammer et al., 2009; Spencer and Deak, 2017). Glucocorticoids themselves activate two classes of receptors, mineralocorticoid receptors and glucocorticoid

Table 1
Descriptions of Rodent Sleep Deprivation (SleepDep) Methodology. Abbreviations: SleepDep (sleep deprivation), TSD (total SleepDep), PSD (paradoxical SleepDep); REM sleep (rapid eye movement sleep), NREM sleep (non-rapid eye movement sleep).

Method Name	Type of SleepDep	Brief Description	Citation
Forced Locomotion	TSD	Constantly rotating treadmills or running wheels keep the animal moving and continuously awake.	Borbely and Neuhaus (1979)
Disk-Over-Water	TSD	An experimental and a yoked control rodent are suspended on a rotating platform over shallow water within the same apparatus. The platform rotates when the experimental animal enters sleep, and if the animal fails to move, it will fall into the water and awake abruptly.	Rechtschaffen et al. (1983); Bergmann et al. (1989)
Gentle Handling	TSD	Animals are passively exposed to mild external stimuli to induce spontaneous exploration in their home cage and promote wakefulness.	Franken et al. (1991)
Air Puffs	TSD	An air puff is delivered into an animal's home cage when NREM or REM sleep is detected.	Grossman et al. (2000); Gross et al. (2015)
Automated Treadmill	TSD	Animals are placed on a rapidly alternating on/off treadmill to keep animals awake. Controls are on a treadmill with a modified and less active schedule.	Guzmán-Marín et al. (2003)
Alternating Platform	TSD	Platforms placed inside a water tank repeatedly submerge and emerge from the water, awakening the animal.	Piérard et al. (2007)
Activity Wheel	TSD	Brief rotation of an activity wheel at regular intervals keeps animals awake.	Christie et al. (2008)
Programmed Rotating Drum	TSD	A circular chamber divided by a clear plexiglass wall houses one rat on either side. A rotating base (drum) keeps the animals continuously awake.	Leenaars et al. (2011)
Grid Over Water	Sleep Fragmentation	Animals are placed on a metal grid floor inside a cage filled with water slightly below the grid surface while controls remain in a cage with sawdust bedding.	Shinomiya et al. (2003)
Programmed Sweeping Bar	Sleep Fragmentation	A horizontal bar, following a programmed scheduled, sweeps the bottom of a normal rodent cage providing mild tactile stimulation to keep animals awake.	Ramesh et al. (2009)
Orbital Shaker	Sleep Fragmentation	Standard laboratory orbital shakers oscillate on a regular schedule to shake animals' home cages and disturb sleep.	Sinton et al. (2009)
Rolling Ball in Tilting Cage	Sleep Fragmentation	Cages placed on moving rockers roll two balls inside the cage to continuously disturb sleep.	Zhu et al. (2012)
Environmental Noise	Sleep Fragmentation	Auditory recordings of various noises (bell, airplane, siren, etc.) are played unpredictably to disturb sleep.	Mavanji et al. (2013)
Flowerpot	PSD	Rodents placed on inverted flowerpots lose their balance at the onset of REM and fall into shallow water, inducing wake.	Jouvet et al. (1964); Cohen and Dement (1965)
Pendulum Technique	PSD	An apparatus moves the animals' cages back and forth in a pendulum motion, causing postural imbalance and brief awakenings that reduce REM sleep.	Van Hulzen and Coenen (1980)
Multiple Platform	PSD	Multiple platforms placed above shallow water force an animal to stay awake and if an animal loses balance upon entering REM sleep, it falls into the water.	Van Hulzen and Coenen (1981)
Direct Midbrain Stimulation	PSD	Direct electrical stimulation of the reticular formation eliminated REM sleep.	Kovalzon and Tsibulsky (1984)
Modified Multiple Platform	PSD	Multiple animals are placed on multiple platforms that lie in shallow water. When an animal enters REM sleep, it loses balance and falls into the water, inducing wakefulness. Social isolation is eliminated.	Nunes Júnior et al. (1994)
Manual Head-Lifting	PSD	The animal's head is lifted by a mechanical lever, triggered by an experimenter, when a REM episode is observed during EEG recording.	Datta et al. (2004)

receptors, throughout the brain and body to regulate energy expenditure to meet real or expected demands. Mineralocorticoid receptors bind glucocorticoids with higher affinity than glucocorticoid receptors and are critically important for regulating circadian and ultradian rhythms of the HPA axis activity. Glucocorticoid receptors, on the other hand, are more important for mediating the effects of glucocorticoids on energy expenditure, inflammation, and neural function (Herman and Tasker, 2016). Under physiological conditions, negative feedback of glucocorticoids on mineralocorticoid and glucocorticoid receptors in the paraventricular nucleus of the hypothalamus and the pituitary gland keeps the HPA axis response under homeostatic control (Jones et al., 1977).

Men and women differentially respond to stress, furthering the importance of including both sexes in research. Reported incidences of stress are higher in women and potentially attributable to underlying differences in stress responsivity (Wellman et al., 2018). For example, compared to men, women exhibit higher baseline respiratory sinus arrhythmia, which correlates more positively with the activities of the sympathetic and parasympathetic nervous systems during an acute stressor (Weissman and Mendes, 2021). Further, sex differences in cortisol responses to acute psychosocial stress are reported in humans (Kirschbaum et al., 1992; Reschke-Hernández et al., 2017). Stress perception and general HPA axis function, however, show high inter-individual variability, making it difficult to determine specifically what sex differences exist (Goel et al., 2014; Rao and Androulakis, 2017; van der Voorn et al., 2017). Even so, women are disproportionately affected by and more vulnerable to stress-related disorders than men, making the consideration of sex in research critical (Dearing et al., 2022).

Sex differences are much more robustly reported in rodents. Like women, female rodents display heightened responses to stress, with greater plasma corticosterone levels than males (Burgess and Handa, 1992; Dalla et al., 2005; KITAY, 1961; Vieira et al., 2018). The pituitary gland is also more sensitive to CRH stimulation and the adrenal glands to ACTH in females than males (Figueiredo et al., 2007; Goel et al., 2014). Females exhibit diminished glucocorticoid receptor-mediated negative feedback control of the HPA axis, which results in slower resolution of stress responses in this sex (Handa et al., 1994). The specific type of stressor should be considered, however, as females are more affected by social isolation whereas males are more affected by trauma exposure (Brown and Grunberg, 1995; Palanza et al., 2001; Pooley et al., 2018).

2. Sex differences in stress responses to sleep deprivation

2.1. Human studies

Mounting evidence suggests that men and women respond differently to SleepDep, including their stress response to losing sleep. Sleep debt, the difference between how much sleep a person needs and how much sleep they get, accumulates more rapidly in women than men, and women may be more susceptible to prolonged wakefulness (Armitage and Hoffmann, 2001; Corsi-Cabrera et al., 2003). As such, women exhibit increased NREM sleep intensity following SleepDep which likely

helps them recover from sleep loss (Armitage and Hoffmann, 2001; Mong and Cusmano, 2016).

2.1. 1. Sympathetic activation

Transitions from an aroused state to NREM sleep typically decrease sympathetic nervous system activity by shifting the autonomic balance to parasympathetic dominant activity, thereby reducing respiratory rate, heart rate and blood pressure (Fink and Dean, 2018). Conversely, regular sleep cycle transitions from NREM to REM sleep, or even brief awakenings from sleep, elicit concomitant increases in the sympathetic nervous system response, blood pressure, and heart rate (Somers et al., 1993). In clinical settings, studying the regulation of autonomic functions following SleepDep serves as a useful tool in understanding the effectiveness of the sympathetic nervous system in both men and women. Following a 24-h period of SleepDep, men exhibited an acute hypertensive response with an increase in blood pressure and a decrease in muscle sympathetic nerve activity (MSNA), indicative of spontaneous sympathetic baroreflex operating point (Carter et al., 2012; Kato et al., 2000). Women, conversely, exhibited potential sympathetic baroreflex dysfunction as they experienced elevated blood pressure with no changes in MSNA (Carter et al., 2012). In older women but not older men, MSNA increased after SleepDep (Carter et al., 2019). Acute SleepDep in young women reduces heart rate variability (HRV), a measure of beat-to-beat changes over time and an index of autonomic nervous system regulation of heart rhythm, and at the same time, decreases HRV low frequency to high frequency ratio which indicates sympathovagal balance (Virtanen et al., 2015).

In women, the association between short sleep duration and risk for cardiovascular disease and diabetes is more pronounced than in men (Cappuccio et al., 2007; Doo and Kim, 2016; Grandner et al., 2018; Kuo et al., 2010; Sun et al., 2016; Tuomilehto et al., 2008; Wang et al., 2015; Zuo et al., 2016). Cardiovascular health is often affected by stress and is critically regulated by the sympathetic nervous system, and studies have more recently recognized sleep as an important contributor (Malhotra and Loscalzo, 2009; Nagai et al., 2010; Somers et al., 2008; St-Onge et al., 2016). Taken together, these results indicate that women may be more vulnerable to negative cardiometabolic consequences of SleepDep (Daugherty et al., 2020; Makarem et al., 2022).

2.1. 2. HPA axis

Sex differences in HPA axis responsivity have also been observed following SleepDep in humans, though most of our understanding of stress responses to SleepDep comes from studies conducted without sex as a powered variable. For example, salivary cortisol and subjective stress are often elevated following SleepDep procedures in humans (Schwarz et al., 2018; Vargas and Lopez-Duran, 2017; Wright et al., 2007) and alterations in glucocorticoid secretion have been previously reported, though sex was often not considered in these studies (Machado et al., 2013; Nollet et al., 2020). Further, subjecting study participants to a psychosocial stress test, such as the Trier Social Stress Test, under control conditions typically induces a rapid elevation in cortisol (Frisch, 2015). However, inconsistent results report the stress response to SleepDep could either blunt cortisol response to a psychosocial stressor, due to the aberrant HPA responsivity, or not differ from the adaptive response seen under normal sleep (Schwarz et al., 2018; Vargas and Lopez-Duran, 2017).

As cortisol varies significantly with time of day, stress responsivity also varies with the time of testing (Krieger et al., 1971). Though sleep condition or sex were not included as variables, key findings revealed that pre-stress salivary and total plasma cortisol levels were higher in the morning and led to a significantly higher cortisol response to stress at this time than when stress took place in the afternoon (Kudielka et al., 2004). These findings posed that the adrenal glands may be more sensitive to ACTH in the morning. On the other hand, under stressful conditions, the HPA axis is suppressed by the vagal tone of the parasympathetic nervous system to reduce the stress response (Thayer and Sternberg, 2006). Higher basal salivary cortisol was associated with lower stress-related increases in salivary and plasma cortisol, despite no differences in heart rate variability, greatly impacted by the cardiac vagal tone, pointing to a blunted HPA response when basal cortisol levels are elevated (Kudielka et al., 2004). These findings critically highlight the significance of considering the impact of the time of day on biological measures of stress responsivity.

The critical need to evaluate sex as a biological variable has only led to modest advancements in our fundamental understanding of the relationship between sleep and the HPA axis activation with a focus on sex differences as very few studies have conducted SleepDep in men and women and measured HPA axis activity. Self-reported good sleep quality compared to poor sleep quality, however, increased cortisol stress responsiveness to psychosocial stress in men but not women (Bassett et al., 2015). Low sleep quality in women the night before an experimental mental stress task did not change cortisol reactivity; however, women with high sleep quality showed high cortisol reactivity (Wright et al., 2007). Importantly, these studies found that sleep quality and not quantity affected cortisol responses to stress (Bassett et al., 2015; Wright et al., 2007). While SleepDep can be a valuable tool for inducing changes in stress responses, it remains essential to also consider long-term sleep quality for health outcomes, though more work is still needed to properly determine if there are sex-specific HPA axis responses to SleepDep in humans.

2.2. Rodent studies

Rodent models have been instrumental in furthering our grasp of neurobiological underpinnings of sex differences in the stress response to SleepDep. Preclinical studies strengthen our understanding by allowing for more comprehensive behavioral, physiological, and biological measurements from experimental subjects. Paradoxical SleepDep has been readily employed to model disruptions related to human sleep loss more closely as it is believed that the disrupted sleep induced by this method, and not merely total sleep loss, may be more representative of what people would experience in daily life.

2.2. 1. Sympathetic activation

Growing evidence has implicated a bidirectional relationship between cardiovascular health and sleep, implicating the sympathetic nervous system in these processes (Jackson et al., 2015; Mullington et al., 2009; Nagai et al., 2010; Tobaldini et al., 2017). Multiple studies have reported variations in cardiac parameters following SleepDep in rodents. The baroreflex sensitivity, a measure of autonomic control of the cardiovascular system, is an important marker for the cardiovascular disease risk (La Rovere et al., 2008). Short-term beat-to-beat modifications in blood pressure trigger the baroreceptor reflex. SleepDep increases heart rate in both sexes but reduces arterial baroreflex-mediated tachycardia in males only (La Rovere et al., 1998; Matos et al., 2013; Rubinger et al., 2012). Numerous studies note an association between elevated low-density lipoprotein cholesterol and increased risk of coronary heart disease (Borén et al., 2020; Ference et al., 2017; Lewington et al., 2007), and SleepDep has also been demonstrated to significantly lower triglycerides and increase high-density and low-density lipoprotein levels in males (Andersen et al., 2004). Ovariectomy in females altered the response to SleepDep such that low-density lipoprotein levels were increased, like in males, and high-density lipoprotein levels remained unchanged in comparison to controls (Antunes et al., 2007). As high-protein lipoprotein levels are inversely associated with cardiovascular disease risk, the impact of SleepDep on outcomes that elevate disease risk appears more detrimental in females compared to males. This notion is further supported by a study wherein both myocardial sensitivity and infarct size are increased, and post-ischemic recovery of contractile function is worsened by SleepDep only in female subjects (Zoladz et al., 2016). Ongoing research continues to support the idea that sleep disruptions are correlated more strongly with the risk for

Table 2
Impacts of sleep deprivation on peripheral corticosterone in studies evaluating female-only or female and male rodent cohorts. All reported effects describe changes from a control condition. Abbreviations: sleep deprivation (SleepDep), gonadectomy (GDX), ovariectomy (OVX), total sleep deprivation (TSD), paradoxical sleep deprivation (PSD).

Length of SleepDep	SleepDep Method	Sample Collection Post-SleepDep	Effect	Species and Strain	Citation
6 h	TSD - Gentle Handling	Immediate (plasma)	Male: No effect Female: No effect	Mouse - Swiss Albino (5w)	Onaolapo et al. (2016)
6 h	TSD - Gentle Handling	Immediate (feces)	Male: No effect Female: No effect	Mouse - C57Bl/6 J	Chiem et al. (2021)
6 h	TSD - Gentle Handling	Immediate (plasma)	Males: No effect **Males GDX: Increase Females: Increase Females OVX: Increase**	Rat - Wistar	Baratta et al. (2018)
20 h	PSD - Modified Multiple Platform	+8 h (serum)	**Male: Decrease** Female: No effect	Mouse - C57Bl/6 J	Buban et al. (2020)
22 h	PSD - Multiple Platform	Immediate (plasma)	Female: No effect	Mouse - BALB/c	Li et al. (2019) *Front.*
24 h	Sleep Fragmentation - Sweeping Bar Chamber (24 h/day)	Immediate (serum)	**Female: Increase**	Mouse - C57Bl/6 J	Mishra et al. (2020)
24 h	Sleep Fragmentation - Sweeping Bar Chamber	Immediate (serum)	**Female: Increase**	Mouse - C57Bl/6 J	Wheeler et al. (2021)
48 h	PSD - Multiple Platform	Immediate (plasma)	**Male: Increase Female: Increase**	Mouse - BALB/c	Gonzalez-Castañeda et al. (2016)
72 h	PSD - Modified Multiple Platform (20 h/day)	+8 h (serum)	Male: No effect Female: No effect	Mouse - C57Bl/6 J	Buban et al. (2020)
72 h	PSD - Multiple Platform	Immediate (plasma)	Male: No effect Female: No effect OVX Female: No effect	Rat - Wistar	Hajali et al. (2012)
96 h	PSD - Multiple Platform	Immediate (plasma)	Male: No effect **Female: Increase**	Mouse - BALB/c	Gonzalez-Castañeda et al. (2016)
96 h	PSD - Multiple Platform	Immediate (serum)	**Female: Increase**	Rat - Wistar	Antunes et al. (2006)
5 days	PSD - Multiple platform (22 h/day)	Immediate (plasma)	**Female: Increase**	Mouse - BALB/c	Li et al. (2019)
8 days	TSD - Gentle Handling (4 h/day)	+15 h (serum)	Male: No effect **Female: Increase**	Mouse - CD1	Murack et al. (2021)
4 weeks	Sleep Fragmentation - Sweeping Bar Chamber (12 h/day)	Immediate (serum)	**Female: Increase**	Mouse - C57Bl/6 J	Wheeler et al. (2021)
8 weeks	Sleep Fragmentation - Sweeping Bar Chamber (12 h/day)	+12 h (serum)	**Female: Increase**	Mouse - C57Bl/6 J	Mishra et al. (2020)
8 weeks	Sleep Fragmentation - Sweeping Bar Chamber (12 h/day)	+7 days (serum)	Female: No effect	Mouse - C57Bl/6 J	Mishra et al. (2020)
9 weeks	PSD - Modified Multiple Platform (8 h/day, 5 days/week)	+3 days (serum)	Female: No effect	Mouse - Swiss Albino	Arora et al. (2021)

cardiovascular dysfunction in females, despite the higher incidence of cardiovascular disease in males (Kappert et al., 2012; Meisinger et al., 2007; Rod et al., 2014).

Important considerations should be made regarding the method of SleepDep, however. The sympathetic system is activated upon physical activity and may be significantly impacted by the way SleepDep is conducted, as some experimental techniques require much more physical activity than others. Further, the extent of sleep disruption, rather than the total amount of lost sleep duration, may be more critical for sympathetic control (Meerlo et al., 2008). For example, restricting total sleep, rather than paradoxical SleepDep, which exclusively eliminates REM sleep, increased mean arterial pressure and reduced bradycardia responses in both sexes (Matos et al., 2013), yet did not increase heart rate, which contrasts the results observed after paradoxical SleepDep (Matos et al., 2013). Taken together, not enough studies have included both males and females and further consideration is thus warranted when evaluating the mechanisms underlying the sex-specific impacts of sleep loss and sleep restriction on the activation of the sympathetic nervous system.

2.2. 2. HPA axis

Activation of the HPA axis and the accumulation of corticosterone in response to SleepDep has been observed in variable degrees in male and female rodents. Historically, studies have overwhelmingly focused on SleepDep experiments in male subjects. To fill the gap in reviewed knowledge, we presently identify studies that evaluated corticosterone elevation in either i) both male and female subjects or ii) females alone. The key findings of these studies are summarized in Table 2.

Historically, studies have found that the gentle handling technique for SleepDep does not elevate corticosterone in male rodents (Nollet et al., 2020). Yet, when 6 h SleepDep was conducted via this method in both males and females, elevated corticosterone was reported in intact females, ovariectomized females, and gonadectomized males but not intact males (Baratta et al., 2018). When this technique is repeated for 8 days, an increase in corticosterone is again reported in females but not males (Murack et al., 2021). Others, however, have used gentle handling and reported no effect on corticosterone in males or females following SleepDep (Chiem et al., 2021; Onaolapo et al., 2016). As it stands, females may be more sensitive to HPA axis activation following SleepDep than males, even when techniques deemed as "gentle" are implemented. However, since the number of studies implementing gentle handling in both sexes remain sparse, more work is needed to validate these findings.

An increase in corticosterone is reported more frequently when other methods of SleepDep are used, such as the flowerpot or modified multiple platform methods used for paradoxical SleepDep (Nollet et al., 2020). As with gentle handling, the first studies to report such findings were conducted only in male subjects. Based on the findings of newer studies that conduct paradoxical SleepDep in females across multiple time periods, corticosterone levels are elevated as well (Mishra et al., 2020; Wheeler et al., 2021). Interestingly, however, several studies that specifically implemented paradoxical SleepDep for 72 h reported no change in corticosterone levels in either males or females (Buban et al., 2020; Gonzalez-Castañeda et al., 2016; Hajali et al., 2012).

The corticosterone increase with SleepDep is transient as circulating levels typically return to baseline under normal physiological conditions that allow for sleep recovery. When plasma samples are taken hours after the conclusion of one day of paradoxical SleepDep, male mice showed decreased levels of corticosterone, below baseline, while female mice showed a return to baseline values (Buban et al., 2020; Li et al., 2019). When corticosterone was assessed at least three days after chronic sleep fragmentation or paradoxical SleepDep, levels of the adrenal-derived hormone were returned to baseline in female mice (Arora et al., 2021; Mishra et al., 2020).

Several studies in mice have evaluated the effects of SleepDep and recovery sleep on responsivity to a stressor. One group reported a reduction in corticosterone in males and an absence of HPA activation in females who underwent one day SleepDep and restraint stress yet decreased corticosterone levels in both sexes following 3 days SleepDep and restraint stress (Buban et al., 2020). When recovery sleep was allowed following paradoxical SleepDep, it was reported that the response to restraint stress was diminished in female but not in male mice (Oyola et al., 2019).

Taken together, corticosterone responses in males and females differ. The nature of these varied responses may, in part, be due to the method employed to induce sleep loss or the duration of sleep loss, as well as subtle species and strain differences. The time between the end of SleepDep procedures and corticosterone measurements also vary greatly across studies, resulting in few replicable findings between groups. Plasma corticosterone levels not only fluctuate with circadian time (Butte et al., 1976; Kakihana and Moore, 1976) but also vary between phases of the estrous cycles, with the highest concentrations during the proestrus and the lowest levels during diestrus (Andersen et al., 2009; Atkinson and Waddell, 1997). In fact, the diurnal variation of cortisol may also vary across the menstrual cycle, such as differences in the timing of peak cortisol levels in the luteal versus follicular phase in women (Parry et al., 1994, 2000). The fact that estrous phase or time of sample collection was not readily accounted for in studies that included females may contribute to the inconsistencies reported in the literature. Further, as human cortisol levels also fluctuate across the menstrual cycle (Duchesne and Pruessner, 2013; Gordon and Girdler, 2014; Hamidovic et al., 2020; Kudielka et al., 2009; Lustyk et al., 2010; Montero-López et al., 2018), noting the estrous phase in experimental rodent models is important to strengthen our translational understanding of underlying mechanisms.

In addition to changes in circulating corticosterone, SleepDep has also been shown to influence adrenal glands, HPA axis target organs, as well as expression and number of glucocorticoid receptors and mineralocorticoid receptors which contribute toward the HPA axis response. The pituitary glucocorticoid receptor and mineralocorticoid receptor relative mRNA expression was reduced in mice of both sexes after longer durations of sleep disruption (Buban et al., 2020). Eight days of 4 h chronic sleep disruption also reduced glucocorticoid receptor protein expression in the hippocampus of male and female mice, with concurrent decrease in number of active glucocorticoid receptor expressing cells in the prelimbic cortex of adult females only (Murack et al., 2021). Regarding ACTH, one study found higher ACTH levels in males than females after 96 h of SleepDep but not 21 days of 18 h/day sleep restriction (Matos et al., 2013). Expression of proopiomelanocortin (*Pomc)* and corticotropin-releasing factor receptor 1 (*Crfr1)* genes, both of which are involved in the HPA axis regulation, was elevated following SleepDep in males and females (Buban et al., 2020). Experimental designs that employ sex as a biological variable when evaluating the impact of SleepDep on HPA reactivity are vastly underdeveloped and underemployed, presently making it quite difficult to definitively conclude the effect of SleepDep on this system in a sex-dependent manner. Future work is warranted to fully characterize the HPA axis response to sleep loss.

3. Sex-specific stress-related consequences of sleep deprivation

The effects of stress associated with sleep loss extend beyond its direct stimulation of the sympathetic nervous system and HPA axis making it important to consider the broader picture. Notably, sleep disturbances and stress lead to a variety of negative physiological and behavioral consequences which can induce or exacerbate disease states. The current section, then, seeks to describe sex-specific endophenotypes that involve stress responsivity and result from aberrant sleep.

3.1. Inflammation

Both stress exposure and SleepDep can activate an immune response and mounting evidence points to the causal involvement of inflammation in various neuronal and behavioral outcomes induced by SleepDep (Arora et al., 2021; Chanana and Kumar, 2016; Haack et al., 2007; Irwin et al., 2008; Streck et al., 2015; Wadhwa et al., 2019; Yin et al., 2017). Inflammatory or autoimmune disorders are up to nine times more prevalent in women than men (Whitacre, 2001) and recent studies looking at the association between sleep and inflammation report differences that are stratified by sex, with women experiencing worse outcomes than men (Irwin et al., 2006, 2008, 2010; Miller et al., 2009; Prather et al., 2013; Suarez, 2008). Poor sleep quality and prolonged sleep latency are associated with increased plasma c-reactive protein and interleukin 6 levels in women but not men (Prather et al., 2013; Suarez, 2008). Further, while both women and men show increased production of the pro-inflammatory cytokines interleukin 6 and tumor necrosis factor α in monocytes following sleep loss and immune stimulation, only women show increases in neurotrophic factor-kB. Elevation in cytokines is sustained into the evening hours in women and correlates with increased circulating inflammatory markers following sleep loss (Irwin et al., 2006, 2008, 2010), collectively suggesting that the immune system responds differentially to sleep loss in women and men.

Interestingly, and in contrast to acute SleepDep performed in the same study that increased cortisol and had no effect on inflammatory markers, chronic circadian misalignment increased levels of circulating inflammatory markers and reduced cortisol (Wright et al., 2015). Similarly, another study conducted with 2.5 weeks of sleep disturbance, characterized by disrupted and shortened sleep, and reported an inflammatory response and reduced cortisol but only in men, as women experienced a reduction in inflammatory markers (Besedovsky et al., 2022). Importantly, these studies highlight the significance of experimental design choices, as SleepDep and sleep fragmentation produced different results regarding the immune response to sleep disruption.

Collectively, preclinical studies have shed critical insight into our understanding of the inflammation that results from acute or prolonged sleep loss, yet limited publications have documented these outcomes in female subjects. A recent report, which included both male and female mice but did not statistically evaluate sex as a biological variable, described an increase in inflammatory genes (*Fos*, *Pgtx2*) and decrease in chemokine (*Ccl5, Cxcl10*), cytokine (*Il-15*), microglia/macrophage (*C3, Tlr1, Trem2*), and interferon genes (*Iipg1, Irf1*) after acute sleep fragmentation (Tapp et al., 2022). Studies conducted work in female-only mice have reported increased proinflammatory markers in the periphery and the brain following sleep fragmentation (Arora et al., 2021; Mishra et al., 2020; Wheeler et al., 2021). A direct role of the sympathetic nervous system in mediating the inflammatory response to SleepDep was mechanistically implicated by pharmacological sympathectomy via peripheral administration of the neurotoxin oxidopamine (6-ODHA), which effectively destroys sympathetic nerve activity (Mishra et al., 2020). However our understanding of the relationship between sleep loss and immune activation remains largely unexplored, particularly with regards to sex-specific immune responses (include big review citations about general sex specific immune responses).

3.2. Learning and memory deficits

It is well understood that sleep is critical for learning and memory (Abel et al., 2013; Diekelmann and Born, 2010; Goel et al., 2009; Havekes et al., 2012; Killgore, 2010; Kim et al., 2022; Kreutzmann et al., 2015; Lim and Dinges, 2010; Walker, 2008; Walker and Stickgold, 2004; 2006). SleepDep and heightened stress are known to independently impair cognitive function, and particularly learning and memory processes. (Alhaider et al., 2011; Ishikawa et al., 2006; Kim et al., 2005; Marks and Wayner, 2005; Romcy-Pereira and Pavlides, 2004). Animal models, which include rodents and non-human primates, have been critical in advancing our understanding of the effects of SleepDep on cognition, learning, and memory (Colavito et al., 2013; Havekes et al., 2015; Rahman et al., 2013, 2017).

In humans, there is high interest in determining the sex-specific effects of sleep loss on cognitive function. According to a meta-analysis study, the effects of sleep restriction negatively affect the cognitive function of men to a greater extent than that of women (Lowe et al., 2017). One smaller study, however, found that SleepDep impaired objective working memory in women, but not men (Rångtell et al., 2019). Thus, there may be sex- and domain-specific cognitive effects of sleep loss (Binks et al., 1999; Corsi-Cabrera et al., 2003; Rångtell et al., 2019). While mechanistic understanding remain elusive, the contributions of circulation sex hormones have been explored (Baker et al., 2019; Genzel et al., 2012; McDevitt et al., 2014; Sattari et al., 2017; Vidafar et al., 2018). Periods of high estrogen levels during the menstrual cycle in women may provide a protective role against SleepDep. Following sleep loss, women in the luteal phase (high estrogen) had similar performance on a psychomotor vigilance task to men, whereas women in the follicular phase (low hormones) had the worst performance (Vidafar et al., 2018). Further, positive associations between sleep and cognition are more profound in high-hormone menstrual phases compared to low (Baker and Lee, 2018; Baker et al., 2019) and after a nap, only men and mid-luteal phase women experienced an increase in NREM spindle activity after learning (Genzel et al., 2012). Thus, alterations in sex hormones, at least in women, may modulate the effects of sleep on cognition.

In rodents, it is well reported that SleepDep impairs learning and memory. Yet to date preclinical studies have predominately included exclusively male subjects, and across studies that include both sexes mixed results are reported, convoluting our overarching understanding of sex differences in SleepDep-induced cognitive dysfunction. A handful of studies note impairments in both sexes following total SleepDep in tasks that probe contextual learning, fear memory, and object recognition, while others report impairments in males, but a resilience in females, in fear extinction and contextual learning (Baratta et al., 2018; Fernandes-Santos et al., 2012; Hunter, 2018). Conversely, males present a resilience to negative attributes of sleep loss in spatial navigation learning and discriminative avoidance, whereas females are distinctly impaired after either acute or prolonged SleepDep (Esmaeilpour et al., 2015; Fernandes-Santos et al., 2012; Hajali et al., 2012, 2015). Studies which have evaluated exclusively female subjects have similarly found that spatial navigation learning across multiple days is impaired with SleepDep, yet object recognition, which relies on a single learning trial, remains intact (Arora et al., 2021; Rajizadeh et al., 2018, 2020a, 2020b; Saadati et al., 2015; Salari et al., 2015; Zagaar et al., 2012). To date, however, there are still very few studies investigating cognitive function in both sexes following sleep loss which make definitive conclusions difficult given the various experimental designs. As our field continues to fill these gaps in knowledge, we should also critically evaluate experimental design details, including the timing that both SleepDep and behavioral testing are conducted, as these factors will critically influence learning acquisition and memory consolidation processes.

Behavioral tasks designed to probe spatial navigation, contextual learning, object recognition, and fear memory are well-documented to rely on the consolidation of information in the hippocampus and extended limbic structures during sleep (Diekelmann and Born, 2010; Ferrara et al., 2012; Marshall and Born, 2007). Thus, it is noteworthy that hippocampal function is often impaired in response to both sleep loss and stress (Kim et al., 2015; Larosa and Wong, 2022; Prince and Abel, 2013; Prince et al., 2014; Walker, 2008). In fact, modest decreases in sleep or even mild disruptions in sleep, without effects on total sleep time, are sufficient to induce deficits in learning and disrupt hippocampal activity (Marks and Wayner, 2005; Van Der Werf et al., 2009). Chronic elevation of glucocorticoids that occurs with prolonged exposure to stress is associated with reductions in neurogenesis in the hippocampus and cognitive impairments (McEwen, 2005; McEwen and Magarinos, 1997)while similar alterations such as reduced hippocampal volume, blunted neurogenesis, altered gene expression, and impaired long-term potentiation in the hippocampus have all been reported following chronic SleepDep (Kreutzmann et al., 2015) As such, disturbances to hippocampal function are likely causally related to learning and memory deficits induced by SleepDep (Havekes et al., 2012; Kreutzmann et al., 2015). Almost all such studies, however, have been conducted in male rodents, so specific effects based on sex currently remain largely unexplored. Given that deficits in cognitive performance, particularly learning and memory impairments, can greatly impact daily functioning it remains of great value to understand the sex-specific changes that occur to these processes following SleepDep. Symptoms such as cognitive impairment and sleep disturbances are also common across a variety of disease states. Elucidating the sex-specific mechanisms underlying these challenges may help identify novel therapeutic targets and allow for more personalized treatment options for patients.

3.3. Mood related changes

In addition to the discussion above, both SleepDep and stress can lead to direct alterations in mood. In fact, insomnia bidirectionally associates with mood disorders and psychiatric illnesses, such that disturbed sleep represents a risk for the onset of disease and is experienced as a symptom during the illness (Breslau et al., 1996; Ford and Kamerow, 1989; Hertenstein et al., 2019; Neckelmann et al., 2007; Palagini et al., 2022a, 2022b). Incidence of insomnia and mood disorders like depression and anxiety are higher in women compared to men (Kessler et al., 1994; Krystal, 2004; Zhang and Wing, 2006) and women may be particularly vulnerable to these disturbances at times of high hormonal fluctuations, such as puberty or menopause (Morssinkhof et al., 2020). Women also appear to be more susceptible to negative emotional responses to SleepDep than men (Birchler-Pedross et al., 2009; van der Helm et al., 2010) as losing sleep has been shown to trigger greater levels of anxiety in women compared to men (Goldstein-Piekarski et al., 2018). In bipolar disorder patients, poor sleep quality is a strong predictor of symptom severity, depressive episodes, and mania in women, but not men (Saunders et al., 2015). Further, perturbations to sleep and subsequent mood may occur more often as comorbidities to other conditions in women than in men. For example, women with cardiovascular disease report an increased burden of insomnia and depression compared to men with the same disease (Jono et al., 2022). Given that stress can also lead to perturbations in emotional states and often affects women more severely than men, outcome measures that reflect alterations in mood may be particularly useful when studying the effects of sleep loss in the context of stress.

Historically, preclinical models have conducted male-centric behavioral studies and noted increased anxiety behaviors following SleepDep (Hajali et al., 2012). Yet more recent studies have reported variable sex-dependent depressive-like and anxiety-like behaviors in rodents following sleep loss. For example, anhedonia, evaluated in the sucrose preference test, increased after 2- or 4-days paradoxical SleepDep in males and females, yet remained unchanged in females who experienced chronic paradoxical SleepDep (Arora et al., 2021; Gonzalez-Castañeda et al., 2016). Further, immobility time in the forced swim test, a measure that indicates depressive-like behavior when elevated,

was reduced in males and females after 2 days of paradoxical SleepDep yet elevated only in females after 4 days of paradoxical SleepDep (Gonzalez-Castañeda et al., 2016). Even still, chronic SleepDep or fragmentation does not consistently induce depressive-like endophenotypes in both sex (Arora et al., 2021; Murack et al., 2021). Anxiety-like endophenotypes have also been inconsistently noted in studies that include both sexes, with reports of no change, increased or decreased anxiety following sleep loss (Arora et al., 2021; Gonzalez-Castañeda et al., 2016; Hajali et al., 2012). When increased anxiety was observed, however, females did display more anxiety behavior than males paralleling what has been observed in human studies (Gonzalez-Castañeda et al., 2016). Finally, grooming, an adaptive behavior to stress (Kalueff and Tuohimaa, 2005), is elevated after paradoxical SleepDep in both sexes, but to a greater degree in males than females (Gonzalez-Castañeda et al., 2016) perhaps indicating greater resilience to sleep loss in males compared to females.

4. Effects of sleep deprivation in the peripartum period

Life experiences such as pregnancy or menopause uniquely affect women. Yet, little remains known about the effects sleep on such events as it relates to women's health. During the peripartum period, women are readily exposed to combinations of psychological and physical stressors, along with fluctuations in mental health with increased incidence of anxiety, depression, and sleep disturbances. With pregnancy, nearly 80% of women report altered sleep (Palagini et al., 2014) and SleepDep is a hallmark feature of the postpartum period during which women are often the primary caretakers of newborn infants (Bornstein et al., 2016). The gestational period is highly vulnerable to endocrine or immunological challenges due to the critical developmental processes that occur during this time. Incidences of SleepDep, then, may be particularly consequential during this period and should be investigated to better protect the health of both mother and child.

In the peripartum period, the resetting of the homeostatic environment often results in poor sleep and elevated stress, which are risk factors for adverse pregnancy outcomes for the mother and child. Epidemiological studies have indicated an increased risk for psychiatric, cardiovascular, or metabolic disorders in individuals whose mothers experienced environmental insults, such as sleep loss, while pregnant. Disrupted sleep during gestation has been associated with increased risk for pre-term delivery, emergency cesarean delivery, and low birth weight (Balserak, 2014; Chang et al., 2010; Micheli et al., 2011; O'Keeffe and St-Onge, 2013; Oyiengo et al., 2014; Reutrakul et al., 2018). Gestational SleepDep has also been associated with higher child body mass index, blood pressure, and an increased risk for obesity, which, when stratified by sex, was worse in girls than boys (Harskamp-van Ginkel et al., 2020). Sleep loss during pregnancy is also associated with an increased risk for gestational diabetes, which may impair insulin sensitivity in the offspring through exposure to maternal hyperglycemia (Damm et al., 2016).

Rodent models have demonstrated direct consequences of maternal SleepDep. At birth, offspring have low birth weight, and increased markers of inflammation, including fetal brain pro-inflammatory cytokines and tryptophan metabolism via the kynurenine pathway (Baratta et al., 2020; Zhao et al., 2014). Offspring from sleep-deprived dams also show a delay in sleep pattern development compared to controls and increased risk-taking behaviors during adolescence (Aswathy et al., 2018a, 2018b; Gulia et al., 2015; Radhakrishnan et al., 2015). In adulthood, hippocampal neurogenesis is reduced after prenatal SleepDep, and offspring show impaired hippocampal long-term potentiation and learning (Han et al., 2020; Khodaverdiloo et al., 2021; Peng et al., 2016; Zhao et al., 2014, 2015). Alterations in immune function are indicated by preclinical reports of increased pro-inflammatory and microglial activation in offspring whose mothers experienced SleepDep during gestation. Further, these offspring express altered sympathetic nervous system and HPA axis activity as variations in sympathetic tone, systolic blood pressure, corticosterone, and glucocorticoid receptors have also been reported (Argeri et al., 2016; Ehichioya et al., 2022; Han et al., 2020; Raimundo et al., 2016; Thomal et al., 2010; Zhao et al., 2014, 2015).

Adverse physiologic responses to SleepDep during pregnancy induce impairments in the intrauterine environment, which can affect the placental function and lead to the observed long-term health consequences for the offspring (Balserak, 2014; Gluckman et al., 2008). By altering neuroendocrine homeostasis, activation of the HPA axis, sympathetic nervous system, or proinflammatory responses contribute to the impact of sleep loss and adverse pregnancy outcomes (Harskamp-van Ginkel et al., 2020). For example, maternal SleepDep increased maternal adrenal weight, proinflammatory cytokines in the placenta, and maternal plasma corticosterone (Baratta et al., 2020; Calegare et al., 2010; Pardo et al., 2016; Thomal et al., 2010). While little remains known about the underlying neurobiology, sleep loss during pregnancy results in sex-specific differential gene expression in the placenta, which may be mechanistically related to the variable health outcomes between sexes (Tarrade et al., 2015).

Beyond the negative outcomes of sleep loss on the intrauterine environment and long-term consequences on offspring development, sleep disturbances during pregnancy can also be harmful to the mother. Despite the large number of studies examining SleepDep during gestation, a significant gap in knowledge remains in understanding the impacts of sleep loss on maternal health outcomes. Short sleep has been associated with an increased risk for hypertensive and metabolic disorders including pre-eclampsia and gestational diabetes, respectively (Edwards et al., 2000; Ekholm et al., 1992; O'Keeffe and St-Onge, 2013; Palagini et al., 2014; Pengo et al., 2018; Williams et al., 2010). Hypertensive disorders of pregnancy are the leading causes of maternal mortality and increase the risk of developing a future adverse major cardiovascular event (Daugherty et al., 2020; Ray et al., 2005, 2017). Gestational diabetes increases the risk of developing type 2 diabetes, which also increases the risk of cardiovascular disease (Bellamy et al., 2009). Thereby, there is a significant clinical need to understanding the contribution of poor sleep outcomes during pregnancy on the development of these chronic conditions in women.

Sleep disturbances and poor sleep quality are also predictive of postpartum depression (Eichler et al., 2019; González-Mesa et al., 2019; Kalmbach et al., 2020; Okun et al., 2018; Poeira and Zangão, 2022; Polo-Kantola et al., 2017). Nearly 85% of women report mild and transient mood disturbances during the first week of postpartum, while 10–15% of mothers meet diagnostic criteria for postpartum depression (Kendell et al., 1981; Ross et al., 2005). Episodes of depression remain common up to two years after birth and can last for more than six months (Cooper and Murray, 1995; Kendell, 1976; Ross et al., 2005; Steinberg and Bellavance, 1999). Children of mothers with postpartum depression are more likely to suffer from behavioral problems, and experience hindered cognitive, emotional, and social development (Murray, 1992). Considering this evidence, diagnosing and treating sleep disturbances during pregnancy remains critical to benefit both the mother and the child. Women who received treatment for insomnia during the third trimester of pregnancy reported fewer symptoms of postpartum depression than those who did not receive treatment (Khazaie et al., 2013). Thus, sleep-based therapies and preventative care may be beneficial in preventing postpartum depression and improving mental health outcomes for mothers.

5. Potential mechanisms underlying sex differences

As described above, sex differences in response to SleepDep have been noted in translational and clinical studies. While recent attention to sex as a critical biological variable in research studies has fostered an increase in publications characterizing the female-specific reaction to SleepDep, more work remains warranted to understand the mechanisms underpinning these effects effectively. The following section will

highlight common pathways and metabolites that regulate sleep and stress in the brain, emphasizing how they are sexually differentiated at baseline and how they may control the response to SleepDep.

5.1. Sex hormones

Sex hormones, steroids classified as androgens or estrogens, are perhaps the most obvious place to start when considering sex differences. Androgens, namely testosterone, are higher in males, whereas estrogens, mainly estradiol and progesterone, are higher in females. These hormones act on steroid receptors and serve both reproductive and non-reproductive functions in the body.

As levels of estrogen and progesterone fluctuate during the female menstrual cycle, special attention is often given to circulating estrogens when considering sex differences and the role of sex hormones. Endogenous forms of estrogen in the circulation include estrone, estradiol, and estriol. As 17β-estradiol (E2) is the primary circulating estrogen in cycling female rodents, preclinical studies aimed at deciphering the contribution of estrogens are generally designed in ovariectomized animals with the reinstatement of E2. While this technique is often implemented to remove the ovaries from female rodents, gonadectomy can also be performed in males with removal of the testes. Techniques such as this provide unique opportunities to manipulate gonadal hormone levels and consequently hormonal signal transduction in a physiological model.

Three classes of estrogen receptors mediate the biological effects of estrogens: estrogen receptors alpha and beta (ERα and ERβ) and the G protein-coupled estrogen receptor. Signaling through the estrogen receptors can alter gene expression through transcriptional effects of nuclear receptors ERα and ERβ or through membrane-bound signaling pathways initiated by binding at all three receptor classes. Activating estrogen receptors at the cell membrane, rather than the nuclear compartment, is critical for rapid synaptic transmission by impacting ion channels and other second messengers. The expression of estrogen receptors in the brain is largely heterogeneous in regions that regulate sleep, including the suprachiasmatic nucleus, hypothalamus, and basal forebrain (Donahue et al., 2000; Rønnekleiv and Kelly, 2005).

Fundamental differences in sleep patterns exist between men and women, even before considering the specific contributions of gonadal hormones. In humans, women frequently report lower sleep quality and more disrupted and insufficient sleep than men (Baker et al., 2020; Groeger et al., 2004; Lindberg et al., 1997; Middelkoop et al., 1996; Mong and Cusmano, 2016; Reyner et al., 1995; Suni, 2022; Zhang and Wing, 2006). Women are also more often diagnosed with sleep disorders than men (Baker et al., 2020; Mong and Cusmano, 2016). Incongruously, however, EEG studies imply that women have higher sleep quality than men, as they exhibit longer total sleep time, shorter latency to sleep onset, and higher sleep efficiency (Baker et al., 2020; Bixler et al., 2009; Carrier et al., 1997; Dijk et al., 1989; Goel et al., 2005; Hume et al., 1998; Polo-Kantola et al., 2016; Reyner et al., 1995; Roehrs et al., 2006; Ursin et al., 2005; van den Berg et al., 2009). While little is known about sleep across the entire menstrual cycle in women, high progesterone and estrogen levels have been correlated with reduced REM sleep (Baker et al., 2012). Further, hormonal contraceptive use is associated with poor sleep quality, reduced sleep efficiency, and increased insomnia symptoms and daytime sleepiness when compared to non-hormonal methods or no contraceptive use (Bezerra et al., 2020; Hachul et al., 2019).

Sex differences in baseline sleep, sleep before experimental manipulations, have also been observed in rodents. Female rodents spend more time awake than males (Ehlen et al., 2013; Koehl et al., 2006; Kostin et al., 2020; Paul et al., 2006; Swift et al., 2020) and when asleep, females spend less time in NREM sleep than males (Ehlen et al., 2013; Franken et al., 2006; Koehl et al., 2006; Paul et al., 2006; Rentschler et al., 2021; Saré et al., 2020; Swift et al., 2020). Some studies have also noted that female rats spend less time in REM sleep than males, a phenomenon that is postulated to be related to cyclic variation of circulating gonadal hormones (Dib et al., 2021; Fang and Fishbein, 1996; Garner et al., 2018; Kostin et al., 2020; Swift et al., 2020). The cyclic alteration in gonadal hormone levels across the female estrous cycle typically produces sleep that is highly variable, with less REM sleep during stages of the cycle where estrogens are high (Dib et al., 2021). Of note, preclinical studies have found that some genetic strains of rodents, such as C57Bl/6 J mice, exhibit sleep patterns that are less variable across the estrous cycle than other strains, or even human sleep across the menstrual cycle (Koehl et al., 2003). However, numerous approaches have been made to reduce or eliminate the circulation of gonadal hormones in rodents to decipher the contribution of these hormones to the observed sex differences in sleep (discussed further below). Even still, it remains difficult to elucidate the exact influence of sex and circulating hormones on baseline rodent sleep.

With respect to gonadal steroids, estrogen modulates sleep in a sex-dependent manner. Female rodents tend to spend more time awake than males as a whole. Yet, gonadectomy, which eliminates circulating gonadal hormones, abolished the sex difference in wakefulness and restored basal reductions in NREM sleep in females (Cusmano et al., 2014; Paul et al., 2006). Further, estrogen given to only gonadectomized females, and not males, increased wakefulness while reinstating estradiol to ovariectomized females reduced various features of NREM sleep including duration, spectral delta power, and slow-wave activity (Cusmano et al., 2014; Deurveilher et al., 2013; Paul et al., 2006; Smith et al., 2022). Regarding REM sleep, estrogens seem to suppress this sleep stage, as females spend less time in REM sleep during stages of the estrous cycle when estrogens are high (Dib et al., 2021). As a whole, estrogens themselves seem to inhibit sleep, as female rodents in proestrus, when estradiol and progesterone levels are highest, show a significant increase in wakefulness and a decrease in sleep compared to any other estrous phase (Hadjimarkou et al., 2008). Further, applied estradiol decreases the activity of the ventrolateral preoptic area, a region that is active during sleep, and the presence of estradiol decreases the expression of adenosine 2 A receptors, which bind adenosine, an endogenous hypnagogic molecule that promotes sleep (Hadjimarkou et al., 2008; Ribeiro et al., 2009). Exogenous estrogen and testosterone also have been shown to alter sleep behavior in females to a greater extent than in males, suggesting a greater sensitivity to gonadal steroids in the female sex (Cusmano et al., 2014). Taken together, these studies indicate that circulating estrogens are in fact important to sex-specific sleep regulation, especially in females.

In response to a SleepDep challenge, the role of estrogens in mediating the homeostatic response appears quite different from basal conditions. Following SleepDep, estradiol-treated rats show more consolidated NREM sleep and increases in total REM sleep in the light phase (Deurveilher et al., 2009; Schwartz and Mong, 2013). While gonadectomy with no hormone supplementation reduces homeostatic responses to sleep loss, estradiol or testosterone treatment potentiates the recovery of REM sleep after acute SleepDep in gonadectomized male rats (Choi et al., 2021; Wibowo et al., 2012). In females, gonadectomy without estrogen supplementation has been shown to improve homeostatic sleep control following SleepDep in mice (Choi et al., 2021). SleepDep also consequently impacts the estrous cycle in female rodents as the initiation of SleepDep during diestrus in rats prolongs this phase during recovery sleep (Antunes et al., 2006). When paradoxical SleepDep is initiated during diestrus, the increase in circulating corticosterone correlates with increased progesterone in these animals (Antunes et al., 2006), suggesting that circulating estrogens relate to the predicted vulnerability to SleepDep-induced stress.

Considering that sleep loss is inevitably stressful, we must consider the interplay between sex hormones and homeostatic stress response. Estradiol treatment in both male and female rodents exposed to stress increased corticosterone and ACTH secretion and impacted the duration of ACTH secretion. Female humans and rodents also have higher basal levels of glucocorticoids, particularly when measured in the morning,

which is hypothesized to be related to the feedback that estrogen provides to HPA axis signaling (Aoki et al., 2010; Larsson et al., 2009; Lundberg et al., 2017; Patchev and Almeida, 1996; Seale et al., 2005; Walf and Frye, 2006). As such, male mice may habituate more effectively to stressful stimuli (Palanza et al., 2001).

Compared to estrogens, less is known about androgens regarding sleep. Testosterone does show a diurnal pattern in humans, with a peak in the morning that progressively decreases across the day (Faiman and Winter 1971; Marrama et al., 1982; Okamoto et al., 1971). In rodents, testosterone also shows diurnal variation though the timing of its peak likely occurs at night (Kinson and Liu, 1973; Leal and Moreira, 1997). Androgens can also modulate the circadian response to light, indicating at least some circadian influence (Karatsoreos et al., 2011; Model et al., 2015). The effects of testosterone regarding direct sleep regulation, however, remain largely unclear (Mong and Cusmano, 2016). Testosterone levels, which may fluctuate during sleep in humans, correlate with REM sleep episodes, REM latency, and sleep efficiency (Kapen et al., 1974; Schiavi et al., 1992). Additionally total SleepDep, but not short partial SleepDep, has been associated with decreased serum testosterone levels in young adult men (Su et al., 2021), though little work has investigated a causative role of testosterone on sleep regulation.

The role of gonadal hormones, and in particular estrogens, is becoming more apparent yet additional consideration is warranted to identify if these factors contribute to sleep regulation or mediate the link between sleep disturbances and stress. However, considering the vast non-reproductive impacts of estrogens and the sex-dependent differences commonly reported in female subjects, considering the impact of circulating estrogen levels on experimental results remains imperative.

5.2. Orexins

Orexins, or hypocretins, are neuropeptides secreted from excitatory neurons localized to the lateral and posterior hypothalamus (de Lecea et al., 1998; Sakurai et al., 1998). The precursor protein prepro-orexin generates the two bioactive orexin peptides, orexin A and orexin B. The primary structure of orexin A is conserved across multiple species, including humans and mice (Sakurai et al., 1998). These peptides act on two G-protein coupled receptors, the orexin 1 (OX1R) and orexin 2 (OX2R) receptors (Marcus et al., 2001; Trivedi et al., 1998). Signaling through orexin receptors is implicated in many processes, including food intake, energy expenditure, motivation and reward-seeking, cognitive performance, memory, and attention and the orexin system is recognized as a major wake-promoting system in the brain. Indirect activation of the orexinergic system, which releases both orexin and glutamate, suppresses sleep-promoting neurons in the ventrolateral preoptic nucleus of the hypothalamus to promote wakefulness and arousal (De Luca et al., 2022). Orexin activity varies across the circadian cycle (Mong and Cusmano, 2016), and lateral hypothalamic orexinergic neurons receive inputs from sleep centers including the median and ventrolateral preoptic areas (Mong and Cusmano, 2016; Taheri et al., 2000). Activation of orexin neurons is highest during wakefulness, likely relating to their role in regulating processes like food intake and energy expenditure. In contrast, the activity of orexin neurons is suppressed during REM sleep (Takahashi et al., 2008), and targeted therapeutic approaches of the orexin system, namely orexin receptor antagonists, are used to promote sleep onset, improve sleep maintenance, and sleep efficiency, and increase total sleep time in individuals with insomnia.

Projections from orexin neurons in the lateral hypothalamus extend to many stress-related brain regions, including the other hypothalamic nuclei, the basal forebrain, amygdala, locus coeruleus, and brainstem (Date et al., 1999), place attention on the orexin system in stress responsivity. Orexigenic projections to the paraventricular nucleus, which act on corticotropin-releasing hormone 1 receptors activate the HPA axis and contribute to neuronal adaptation to severe or chronic stress (Berridge et al., 2010; Johnson et al., 2012; Kirouac et al., 2005; Winsky-Sommerer et al., 2004). Orexins promote the release of ACTH and stimulate glucocorticoid secretion from the adrenal glands (Date et al., 2000; López et al., 1999; Mazzocchi et al., 2001; Ziolkowska et al., 2005). Orexins also activate the sympathetic stress responses, increasing blood pressure, heart rate, and sympathetic nerve activity (Shirasaka et al., 1999; Smith et al., 2002).

Recent research has also placed attention on sex differences in the orexinergic system. Orexin neurons in the lateral hypothalamus are highly sensitive to fluctuations in estrogen levels (Mong and Cusmano, 2016). Further, increased glucocorticoids act directly on the orexin promotor in females to increase prepro-orexin expression (Grafe et al., 2017; Silveyra et al., 2010), suggesting a sex-specific regulation of the orexin system. Orexin 2 receptor expression in the paraventricular nucleus is higher in females than males, which may be related to exacerbated stress responses in females (Grafe and Bhatnagar, 2018; Loewen et al., 2017). Human studies have also demonstrated higher basal levels of orexin in the cerebrospinal fluid and immunoreactivity of postmortem brain regions including the prefrontal cortex and anterior cingulate cortex in women compared to men (Grafe et al., 2017).

Orexins may play a causal role in behavioral endophenotypes of stress and sleep disruption. Psychiatric disorders commonly describe changes in arousal or stress responsivity, like anxiety. Direct effects of orexin in the thalamus and brainstem induces anxiety-like behavior, evidenced by altered performance in the social interaction test and elevated plus maze in rats (Heydendael et al., 2014; Li et al., 2010; Lungwitz et al., 2012). Orexins have also been shown to promote depressive-like behaviors following stress, and clinical research has demonstrated reduced diurnal variation in cerebrospinal fluid orexin in patients with major depressive disorder (Salomon et al., 2003). As discussed above, the wake-promoting effects of corticotropin-releasing hormone and ACTH are plausibly mediated via orexinergic neurons, suggesting a mechanistic link between sleep disturbances and stress responses in mood disorders (Chastrette et al., 1990; Ehlers et al., 1986; Opp et al., 1989; Winsky-Sommerer et al., 2004). Psychiatric disorders such as anxiety, depression, and post-traumatic stress disorder disproportionally affect women (Altemus et al., 2014), placing critical attention on further research that could leverage the use of therapeutic avenues like orexin receptor antagonists to treat conditions that include sleep and stress disturbances.

5.3. Circadian timing systems

Like sleep homeostasis, the circadian system can also contribute to the basal activity of the HPA axis. The suprachiasmatic nucleus sends projections to the pituitary gland and other hypothalamic centers to directly regulate the HPA axis and glucocorticoid release. In the hypothalamus, the suprachiasmatic nucleus regulates HPA activity by inhibiting neurons that secrete corticotropin-releasing hormone. The suprachiasmatic nucleus can also modulate the stress response indirectly through autonomic nervous system connections to the adrenal cortex. Further, glucocorticoids have a diurnal release pattern indicating circadian influences, with peak cortisol arising at the onset of the active phase in humans (Allada et al., 2017).

Differences in the circadian system between males and females may precipitate sex differences observed following SleepDep. Anatomically, the suprachiasmatic nucleus in males is larger and contains more axospinal synapses, postsynaptic density material, asymmetrical synapses, and vasoactive intestinal peptide (VIP)-expressing neurons than females. Functionally, the spontaneous firing rate in VIP neurons is higher in males than females in the light phase, whereas in females suprachiasmatic nucleus neurons have higher thresholds for evoking action potentials in the dark phase than males. These anatomical and functional differences between sexes may help explain sex-specific effects that occur across time of day in studies that include both males and females.

Behaviorally, women tend to wake up and go to bed earlier than men and have shorter circadian periods of body temperature and melatonin

rhythms (Cain et al., 2010; Duffy et al., 2011; Wever, 1984). Women also typically exhibit earlier melatonin peaks with larger amplitudes than men (Adan and Natale, 2002; Boivin et al., 2016; Cain et al., 2010; Campbell et al., 1989; Lehnkering and Siegmund, 2007; Mongrain et al., 2004; Putilov, 2015; Roenneberg et al., 2007; Santhi et al., 2016; Tonetti et al., 2008; Vitale et al., 2015). Basal corticosterone levels are higher in female rodents than males and are frequently correlated with female estrogen levels. Taken together, the circadian timing system is sexually differentiated and regulates sleep and stress processes. Baseline differences in the circadian system may contribute to the divergent effects of SleepDep in males and females, and we strongly advocate for comprehensive experimental design in preclinical studies that consider the timing of experiments to thoroughly evaluate neurobiological underpinnings.

5.4. Astrocytic neuromodulation

Glial cells serve unique functions in the brain and are critical in the regulation of homeostatic processes. Astrocytes, the most abundant neuroglia type in the brain, are uniquely positioned to integrate and modulate neuronal responses and possess the ability to synthesize and release neuromodulators that directly influence neural firing (Araque et al., 2014; Santello et al., 2012). Astrocytes can regulate synaptogenesis, neurogenesis, ion regulation neuronal migration, synaptic transmission, and modulate neuroendocrine functions (Jauregui-Huerta et al., 2010; Kurosinski and Götz, 2002). Increasing evidence implicates astrocytes in the regulation of sleep homeostasis and stress responsivity and astrocytes likely serve multiple functional roles in these regards. Thus, critical consideration of the role of neuroglia like astrocytes in the neurobiology of sleep loss is timely and warranted.

Stress exposure also produces variable and brain region-specific effects on astrocyte activation, suggesting a complex regulatory process (Bridges et al., 2008; Lambert et al., 2000; Leventopoulos et al., 2007; Nichols et al., 1990; O'Callaghan et al., 1991; Ramos-Remus et al., 2002). For example, some studies report a reduced number and density of glial cells and reduced glial fibrillary acidic protein (GFAP) expression, a histological marker of astrocytes, following corticosterone treatment or psychosocial stress (Banasr et al., 2010; Czéh et al., 2006; Nichols et al., 1990; O'Callaghan et al., 1991) while others report increases in GFAP immunoreactivity following restraint stress in the hippocampus (Jang et al., 2008; Kwon et al., 2008). Altered expression of proteins such as connexin 30 and 43 (gap junction proteins), aquaporin 4 (a water channel protein), S100β, (a calcium-binding protein (Margis et al., 2004; Scaccianoce et al., 2004), and amino acid transporters 1 and 2 have also been reported in astrocytes following stress exposure (Rajkowska et al., 2013). These alterations could indicate potential dysfunction in astrocytic processes such as metabolic clearance and calcium signaling and may contribute to the negative effects of stress. Moreover, glucocorticoid and mineralocorticoid receptors are expressed on astrocytes and glucocorticoids have potent effects on astrocytic function (de Kloet, 2003; De Kloet et al., 1998; Jaferi et al., 2003; Jauregui-Huerta et al., 2010). Glucocorticoid-induced astrocytic dysfunction may prevent optimal glutamate clearance from the extracellular space, and therefore promote excitotoxicity, an effect commonly seen following chronically elevated glucocorticoids (Pearson-Leary et al., 2015; Popoli and Pepponi, 2012). Astrocytes also critically mediate the effects of stress on neurogenesis and learning and memory, especially in the hippocampus (Luarte et al., 2017; Pearson-Leary et al., 2015).

During sleep, astrocytes play multiple functional roles, including the clearance of accumulated debris and metabolites, a critical process that protects neuronal function and homeostatic maintenance. The process of glymphatic clearance exchanges interstitial fluid with cerebrospinal fluid through aquaporin-4 water channels in astrocytes (Absinta et al., 2017; Aspelund et al., 2015; Eide and Ringstad, 2015; Iliff et al., 2012, 2013; Iliff and Nedergaard, 2013; Kiviniemi et al., 2016; Louveau et al., 2015). This process is highly controlled by the sleep-wake cycle and is primarily active during slow-wave NREM sleep and suppressed during wake (Reddy and van der Werf, 2020; Xie et al., 2013; Yan et al., 2021). Proper clearance of waste in the CNS, like neurotoxic proteins beta-amyloid and tau, is crucial as imbalances in this process can lead to neurodegeneration and progression of disease pathology (Abbott et al., 2018; Plog and Nedergaard, 2018).

Brain metabolism is also highly controlled by astrocytes during the sleep-wake cycle. The very high energy demands of the brain account for a disproportionately high, almost 20%, amount of total body metabolism, and the demand is significantly higher during wakefulness compared to sleep (Attwell and Laughlin, 2001; Bellesi et al., 2018; Karnovsky et al., 1983). Glucose, the main source of physiological energy, is stored as glycogen exclusively in astrocytes in the brain (Obel et al., 2012). Glycogen stores which are depleted during wakefulness are hypothesized to replenish within astrocytes during sleep (Bellesi et al., 2018; Benington and Heller, 1995; Karnovsky et al., 1983; Scharf et al., 2008). Further, glycogen depletion during sustained wakefulness has been linked to a buildup of sleep pressure itself (Bellesi et al., 2018), pointing to a mechanism through which astrocytes may induce homeostatic sleep drive, process S.

Astrocytes may also regulate sleep need, strengthening their significance as part of the sleep homeostat. Impairing gliotransmission from astrocytes decreases slow-wave activity, an indicator of sleep pressure (Halassa et al., 2009). Further, astroglial calcium signals during NREM sleep change in proportion to sleep need and reducing intracellular calcium in astrocytes impairs homeostatic responses to SleepDep (Ingiosi et al., 2020). Conversely, sleep also affects glial function and influences the morphology, gene expression, gliotransmitter release, and proliferation of glial cells like astrocytes (Brancaccio et al., 2017; Frank, 2019; Marpegan et al., 2011; Svobodova et al., 2018; Womac et al., 2009), as well as astrocytic interactions with neurons, which dynamically changes across the sleep-wake cycle (Blum et al., 2021; Bojarskaite et al., 2020; Fellin et al., 2012; Halassa and Haydon, 2010; Ingiosi and Frank, 2022; Ingiosi et al., 2020; Jha et al., 2022; Petit et al., 2015; Tsunematsu et al., 2021; Vaidyanathan et al., 2021). Astrocytes can extend or retract processes during sleep or wakefulness, respectively, which may be important to the regulation of sleep (Araque et al., 2001).

It has been shown that astrocytes within the SCN can influence circadian rhythmicity, potentially by contributing to the hypothesized circadian regulator, process C (Astiz et al., 2022). In cultured SCN brain slices, astrocytes are essential to maintain circadian synchrony (Schinohara, 1995) (Barca-Mayo et al., 2017; Prosser et al., 1994) and in vivo studies have implicated SCN astrocytes as critical time-keepers for the body (Astiz et al., 2022; Barca-Mayo et al., 2017; Brancaccio et al., 2017, 2019; Tso et al., 2017). Astrocytes express the molecular clock machinery and show self-sustained and entrainable circadian rhythms that remain independent of neuronal interactions (Barca-Mayo et al., 2017; Marpegan et al., 2009; Prolo et al., 2005). While not inherently linked to sleep or stress directly, the influence of the circadian timing system through astrocytes may be an important modulator of the effects of SleepDep and its contribution should be considered in future studies.

Yet, while little remains known about the sex-specific roles of astrocytes in sleep homeostasis, at least some features of astrocytes appear different based on sex (Conejo et al., 2003; McCarthy et al., 2003) and may inform future studies. For example, in males, astrocytes present in greater numbers or with greater GFAP immunoreactivity in the hypothalamus and CA3 of the hippocampus (Johnson et al., 2008; McCarthy et al., 2003; Mohr et al., 2016; Mong and McCarthy, 2002), while in females there are more GFAP immunoreactive astrocytes in hippocampal CA1 and dentate gyrus (Arias et al., 2009; Conejo et al., 2003). Astrocyte morphology within the hippocampus, which is critical sleep and stress responses as previously described, may contribute to functional differences, though future study is warranted. Further, astrocytes express both ERα and ERβ receptors and can thus directly respond to estradiol, which is implicated in various neuroprotective roles in the

brain (Acaz-Fonseca et al., 2014; García-Ovejero et al., 2002; Roque and Baltazar, 2019; Wilson et al., 2002). Taken together, there are features of neuroglia that are differentiated by sex, though potential sex-specific functional differences require additional investigation.

5.4.1. *Astrocyte-derived gliomodulators and sleep*

Unique neuromodulators are synthesized within astrocytes that have been implicated in modulating sleep-wake homeostasis. Astrocyte-derived metabolites such as adenosine and kynurenic acid (discussed below) serve critical roles for sleep in the brain. Disruptions in the levels of these metabolites have been associated with disease states which include sleep disruption as a symptom. As such, the consideration of astrocyte-derived neuromodulators in the etiology of sleep-related conditions, including sleep loss, is warranted.

5.4.1.1. Adenosine. ATP degradation in the brain can occur within astrocytes to generate adenosine. Adenosine accumulates during wakefulness and increases after SleepDep in the brain (Porkka-Heiskanen et al., 1997; Strecker et al., 2000), key evidence that has placed attention on adenosine as a regulator of homeostatic sleep need (Bjorness et al., 2016; Brown et al., 2012). Adenosine also acts as an endogenous somnogen (Porkka-Heiskanen and Kalinchuk, 2011), as direct infusion of adenosine or its receptor agonists into key brain regions promotes sleep through actions on adenosine 1 and adenosine 2 A receptors (Gallopin et al., 2005; Huston et al., 1996; Kim et al., 2020; Kumar et al., 2013; Liu and Gao, 2007; Methippara et al., 2005; Porkka-Heiskanen et al., 1997, 2000; Ticho and Radulovacki, 1991; Zhang et al., 2013). Activation of adenosine 1 receptors inhibits several wake-promoting areas of the brain such as the cholinergic brain stem and basal forebrain, orexinergic lateral hypothalamus, and histaminergic posterior hypothalamus to promote sleep (Alam et al., 1999; Liu and Gao, 2007; Oishi et al., 2008; Rainnie et al., 1994). Alternatively, activation of adenosine 2 A receptors increases the excitability of sleep-active GABAergic neurons in the hypothalamus to suppress activity of arousal-related areas of the brain (Alam et al., 2014; Choi et al., 2022; Kim et al., 2020; Kumar et al., 2013; Scammell et al., 2001). Caffeine, a widely used stimulant, exerts its alerting effects by antagonizing adenosine 2 A receptors (Huang et al., 2005; Reichert et al., 2022). Adenosine administration also lengthens circadian periods by increasing *Per1* and *Per2* gene expression (Jagannath et al., 2021), thereby modulating circadian regulation. Inhibition of adenosine signaling, like with caffeine, enhances the phase-shifting effects of light whereas adenosine agonists diminish the impact of light (Burke et al., 2015; Jagannath et al., 2021), showing that light signaling to the molecular clockwork can be directly altered by adenosine signaling. Recent evidence demonstrates that estrogen can block adenosine signaling in the median preoptic nucleus and attenuate the local effects of adenosine 2 A receptors in this brain region (Smith et al., 2022). This action on adenosine may underly estrogenic suppression of sleep behavior seen in female rodents.

Further, alterations in adenosine, adenosine receptors, and extracellular ATP have been observed after exposure to acute and chronic stressors (Coelho et al., 2014; Crema et al., 2013; Latini and Pedata, 2001; Zimmermann et al., 2016). Blockade of adenosine 2 A receptors ameliorates hippocampal and spatial memory deficits following acute or early life stress in rodents (Batalha et al., 2013; Cunha et al., 2006), suggesting a role for hippocampal adenosine receptors in stress-induced modifications, especially with regards to cognition. As alterations in these receptors are displayed in a variety of clinical conditions and progressive aging (Cunha, 2005; Cunha et al., 1995; Lopes et al., 1999a, 1999b; Meerlo et al., 2004), blockade of adenosine 2 A, in particular, may be a useful therapeutic strategy.

5.4.1.2. Kynurenic acid. Kynurenic acid, an astrocyte-derived metabolite of the kynurenine pathway of tryptophan degradation, is an endogenous antagonist of glutamatergic and cholinergic neurotransmission. Of note, kynurenine pathway metabolism is enhanced in response to stress (Badawy, 2017; Klausing et al., 2020; La Torre et al., 2021; Martín-Hernández et al., 2019; Notarangelo and Schwarcz, 2016) and dysregulation of the pathway occurs in various psychiatric and neurological disorders where sleep disturbances are reported as a symptom (Bilgiç et al., 2022; Erhardt et al., 2017; Gorgoni et al., 2020; Klingaman et al., 2015; Missig et al., 2020; Pocivavsek et al., 2016; Pocivavsek and Rowland, 2018; Robinson-Shelton and Malow, 2016; Sathyasaikumar et al., 2011). Pathophysiological evidence thereby suggests that elevations in kynurenic acid may contribute to symptom severity and sleep dysregulation (Pocivavsek et al., 2017; Rentschler et al., 2021; Wright et al., 2021). Of note, preclinical studies have demonstrated that elevated kynurenic acid reduces REM sleep and impacts arousal phenotypes (Milosavljevic et al., 2023; Pocivavsek et al., 2017; Rentschler et al., 2021). On the other hand, acute SleepDep also elevates kynurenic acid in the brain, notably in the hippocampus, and exacerbates cognitive dysfunction in males compared to females (Baratta et al., 2018). However, SleepDep during pregnancy has been shown to stimulate kynurenic acid production in fetal brain tissue and this phenomenon is directly related to an increase in maternal plasma corticosterone and placental proinflammatory cytokines (Baratta et al., 2020). Higher levels of glucocorticoids during SleepDep are postulated to affect kynurenine metabolism and lead to enhanced kynurenic acid (Bhat et al., 2020; Gibney et al., 2014; Miura et al., 2008a, 2008b). The negative consequences of these elevations, such as suppressed neurogenesis in the hippocampus (Bhat et al., 2020; Guzmán-Marín et al., 2003; Kanai et al., 2009) remain to be fully elucidated.

6. Conclusion

As discussed, common neurobiological results between sleep loss and stress point to common mechanisms by which these processes can lead to disease. A thorough understanding of the changes induced by both sleep and stress can potentially allow for intervention strategies, including therapeutics, that can target malfunction caused by either stress or sleep loss. We presently highlight many advancements in our understanding over decades of sleep and stress research. Our current understanding points to a number of sex differences which suggest a higher degree of responsivity to disrupted sleep in females compared to males in outcomes such as HPA reactivity, sympathetic nervous system activation, cardiovascular dysfunction and mood-related changes (Fig. 3). Yet, throughout the present review we point to many remaining pitfalls in our comprehensive understanding of sex-specific responses and underlying mechanisms. This creates critical need to support studies that consider the intersection of sex, and gender, in sleep- and stress-related outcomes. Translationally relevant experimental systems provide a depth of opportunity to probe these mechanisms. Taken together, losing sleep is stressful. Yet given the known connection between stress and sleep, it appears possible that health outcomes associated with stress may actually benefit from prevention and treatment strategies focused on improving sleep.

CRediT authorship contribution statement

Courtney J. Wright: Conceptualization, Writing – original draft, Writing – review & editing, Visualization. **Snezana Milosavljevic:** Conceptualization, Writing – original draft, Writing – review & editing, Visualization. **Ana Pocivavsek:** Conceptualization, Writing – original draft, Writing – review & editing, Visualization, Supervision, Funding acquisition.

Declaration of competing interest

No conflicts of interest to report

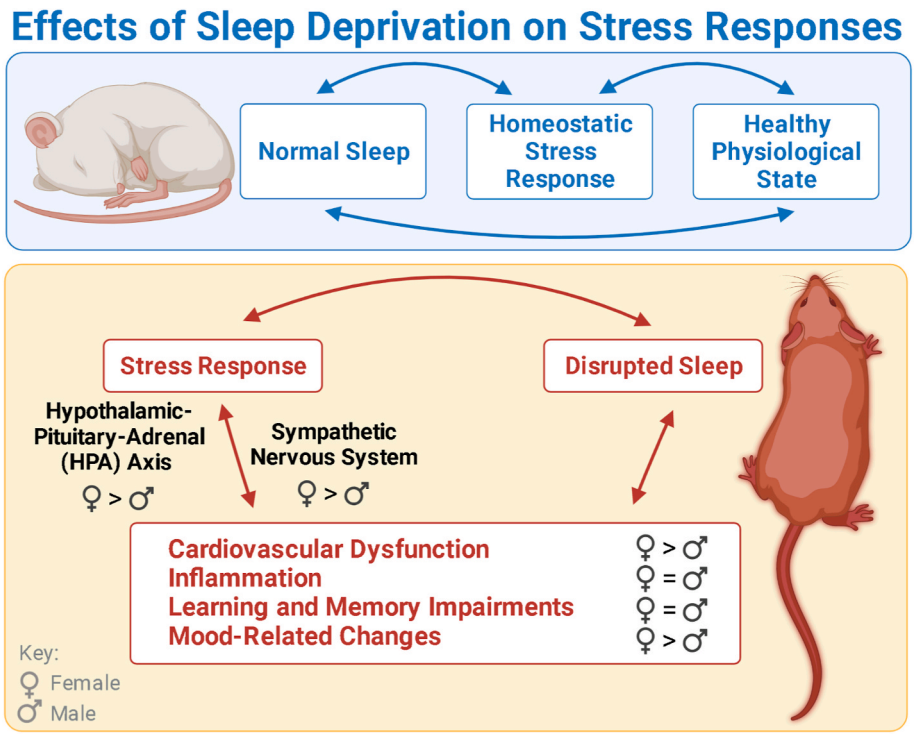

Fig. 3. Effects of sleep deprivation on stress responses. Summary schematic of data discussed in the article which finds sex-specific responses to sleep loss.

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