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Perspective

Sleep and the recovery from stress

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SUMMARY

The relationship between stress and sleep is multifaceted, with stress capable of both disrupting and promoting sleep depending on the nature, intensity, and duration of the stressor. While stress commonly leads to sleep fragmentation and arousal in both humans and animals, certain selective stressors, such as immune challenges and psychosocial stress, promote sleep in rodent models. Specific neural circuits, such as those involving the ventral tegmental area and lateral habenula, mediate this stress-induced sleep. Post-stress sleep may facilitate recovery, reduce anxiety, and enhance stress resilience, but the extent to which sleep versus wakefulness post-stress aids long-term adaptation is unclear. Both human and animal studies highlight a bidirectional relationship, where stress-induced changes in sleep architecture may have adaptive or maladaptive consequences. Here, we propose that post-stress sleep contributes to resilience and discuss potential mechanisms underlying this process. A deeper understanding of these pathways may provide new strategies for enhancing stress recovery and improving mental health outcomes.

INTRODUCTION

Sleep is a naturally occurring, unconscious yet arousable state in which we experience dreams while remaining essentially disconnected from the external world.[1] Despite its perceived benefits, there is no clear consensus in the literature on whether sleep primarily benefits the brain, body, or both.[2–10] A fundamental question remains: does sleep reflect a singular physiological process, multiple distinct processes, or is it primarily an adaptive behavior that varies across species according to ecological niche, food availability, and lifestyle?[3] At least for humans, the undeniable importance of sleep is clear. Many deficits appear following a night of missed sleep,[5,11] including heightened stress responses.[11,12]

Both humans and rodents exhibit a homeostatic drive for sleep, wherein prolonged wakefulness leads to an increased pressure to sleep—an urge that ultimately becomes irresistible.[13] This compensatory response suggests that sleep serves an essential function. As the extent of sleep deprivation rises, the level of stress increases. In mice, sustained sleep deprivation can trigger a cytokine storm, ultimately leading to death.[14] While sleep deprivation imposes physiological stress, stress itself can also disrupt sleep, often creating a vicious cycle in which stress-induced arousal impairs sleep initiation and maintenance.[15–23] Despite the vulnerability of sleep, arousability remains a critical component of its function. The ability to awaken in response to potential threats is evolutionarily advantageous.[24] Even during non-rapid eye movement (NREM) sleep, the neocortex processes external stimuli, albeit with reduced effectiveness.[25] Similarly, individuals can respond to commands during rapid eye movement (REM) sleep,[26] and animals can be preferentially awakened from REM sleep by predator scent.[27] One of the key neural systems coordinating arousal from sleep is the widely projecting noradrenergic (NA) system in the locus coeruleus (LC) in the brainstem. Optogenetic silencing of LC^{NA} neurons in rats reduces the effectiveness of auditory stimuli in producing arousal from NREM sleep,[28] while stimulation of LC^{NA} terminals in the lateral preoptic (LPO) area of the hypothalamus induces immediate awakening.[29] Multiple other neural pathways also facilitate arousal in response to threatening stimuli.[30–32]

Importantly, stress can hijack arousal circuits, contributing to sleep disturbances.[33] In both humans and other mammals, various forms of stress induce anxiety and disrupt sleep by activating wake-promoting systems,[22,34–36] including the LC^{NA} pathway. The causes underlying sleep loss are clearly numerous. Indeed, most stressors and trauma often promote wakefulness,[15–22,36–38] prolong sleep onset latency, fragment sleep architecture, and degrade overall sleep quality[39,40] (see Box 1 for more examples). External and internal stimuli, such as noise, temperature fluctuations, and chronic pain, frequently cause micro-arousals (MAs), disrupting sleep continuity.[40,94,95] While brief MAs are common and may even support cognitive function,[95,96] excessive sleep fragmentation is considered more detrimental to both mental and physical health than total sleep loss.[39,97] However, rather than focusing on stress-induced insomnia, this article explores a less conventional phenomenon: stress-induced sleep. Understanding this paradoxical response may provide insights into the fundamental functions of sleep and offer potential strategies to harness sleep as a protective mechanism against the adverse effects of stress.

SLEEP AS A RESPONSE TO STRESS

Stress serves as an organizing framework for a broad range of phenomena related to both human and animal adaptation.[98] Stress

Box 1. Stressor paradigms: Insomnia and sleep

Animal models are essential to look for mechanisms. There are various kinds of stress models used in rodents.[41] Physical stressors (e.g., electric foot shock and forced swim) produce immediate and potentially life-ending threats, and on the other hand, psychological stressors (immobilization, noise, and SDS) involve discomfort and anticipation of physical pain and/or fear.[41,42] For example, putting mice in a tube or restraining apparatus for 5–10 min sustains wakefulness when the animal starts to sleep.[43] We highlight two specific experimental examples linking stress and insomnia in more detail below.

INSOMNIA AND THE "FIRST-NIGHT EFFECT"

For some people, acute insomnia occurs in a new environment.[44] This is the so-called "first-night" effect: it takes longer to get to sleep (increased sleep latency), and there is less time asleep on the first night of testing.[44] As a mild stress, the cage change strategy for rodents can mimic the first-night effect in humans.[45] For example, placing a rat in a cage that was previously occupied by another rat makes it harder for the new occupant to initiate sleep.[22,46] Similar effects can be obtained with mice, simply by placing them in a clean cage with fresh bedding,[45,47,48] or changing the cage once an hour.[49]

INSOMNIA INDUCED BY SDS

SDS is an ethological model in male rodents that mimics fights over territory and mates. It is a type of natural psychosocial stress that could resemble low social status, social exclusion, and bullying in humans.[50] SDS is conducted by using the "resident-intruder" paradigm, in which male rodents are placed in the cage of a male aggressor, and animals are allowed to fight freely.[42,51–54] SDS is a rich paradigm that produces many long-term changes in behavior that may reflect increased anxiety and depression. After SDS, animals show less social interaction but can be grouped as resilient and susceptible to the SDS challenge.[53,55] SDS induces changes in the brain circuitry and neurochemistry of defeated animals.[52] Depending on the SDS protocol, and there are many variables,[53] such as acute and chronic protocols, SDS can induce either wakefulness or sleep in defeated animals.[34,53,56,57] SDS induces insomnia if the mice are placed in a different sleep environment, rather than in their homecages, after stress[34] or if mice become injured during fighting. For example, SDS also fosters insomnia if bullied mice try to sleep in the presence of the aggressor mouse but are separated by a partition but still in visual and olfactory contact with the agressor.[34]

SLEEP INDUCED BY SDS

Many studies have demonstrated that SDS in male rodents enhances sleep, particularly NREM sleep, with increased delta power indicating deeper sleep states.[56–60] SDS prolongs the duration of NREM sleep in both mice and rats.[51,57,59,61–63] Additionally, certain SDS protocols also enhance REM sleep.[51,57,62,64,65] Remarkably, even a brief 10-min SDS session in mice can induce a period of "sleep-like inactivity."[66] Chronic SDS regimens conducted over 10 days consistently elevate both NREM and REM sleep, with NREM sleep returning to baseline levels after the stress period while REM sleep remains elevated[64] (Figure 1B).[64] Intriguingly, the males of certain species of *Drosophila* flies also sleep longer after forced interaction,[69] which might be a conserved form of stress-induced sleep.

SLEEP INDUCED BY IMMOBILIZATION

Both NREM and REM sleep are enhanced in rodents subjected to immobilization stress,[70–72] and variations of restraint stress (RS) protocols (single or multiple episodes) consistently increase REM sleep.[72–75]

SLEEP INDUCED BY UCMS

UCMS involves subjecting animals, typically rodents, to a series of mild and unpredictable stressors over an extended duration, consistently increasing REM sleep throughout the experimental period (Figure 1C).[67]

PTSD AND SLEEP

Post-traumatic stress disorder (PTSD) only applies to humans but is modeled in rodents using the single prolonged stress (SPS) paradigm. This protocol involves restraint, forced swimming, and exposure to unpleasant odors. Findings from studies using the SPS model vary: some indicate an initial decrease in NREM sleep delta power, followed by subsequent increases and sustained elevation of both NREM and REM sleep for several hours post-SPS,[76,77] followed by a sustained reduction in both NREM and REM sleep, lasting approximately 2 days.[77] Chronic stress induced by repeated exposure to air puffs, foot shocks, and restraint can also elevate subsequent NREM sleep.[78,79] Furthermore, alternative PTSD models, like foot shock in mice, increase NREM or REM sleep

(Continued on next page)

Box 1. *Continued*

in response to stress.[68,80,81] Chronic RS (3 to 4 h per day) over 2 weeks also increases REM sleep duration and the magnitude of theta power.[82]

EARLY LIFE STRESS AND REM SLEEP

Early life stress, such as prenatal RS, maternal separation, providing only limited nesting material to the mother, or cross-fostering, enhances REM sleep in adult rats, leading to persistently increased REM sleep levels, with varying degrees of effect.[83–89]

HUMAN MODELS OF EMOTIONAL STRESS LINKED TO SLEEP

VR provides an elegant approach for investigating the relationship between stress and sleep. For example, participants can undergo a simulated public speaking task using VR headsets while physiological stress markers, such as heart rate and cortisol levels, are measured. Subsequent sleep parameters, including EEG recordings, can then be analyzed to assess the impact of stress on sleep architecture[90] (Figure 2D). Volunteers can also be shown disturbing film clips (e.g., of car crashes with severely injured people), and this viewing subsequently produces intrusive memories.[93] In a typical study, straight after the film clip, subjects were either allowed to nap for 90 min, while controls stayed awake, had a snack, or took a walk.[92] Participants then noted in an "intrusion diary" the number of intrusive memories about the film in the subsequent week[92] (Figure 2E).

can be defined as "a state of perturbed homeostasis resulting from perception of endangerment."[99] Psychologically, stress is conceptualized as "a relationship between an individual and their environment, in which the individual perceives the demands to exceed their resources, thus threatening their well-being."[98] This definition is also applicable to animals. If we use the perturbed homeostasis interpretation of stress, it can be extended to the cellular level and illness, highlighting its pervasiveness across biological systems, and of course, stress encompasses a spectrum of negative emotional and psychological experiences from everyday challenges to traumas such as accidents or combat. Only relatively few stressors induce sleep, and these stressors incorporate illness and intense emotions, perhaps suggesting there could be some core molecular commonalities produced in these states that then act on sleep-inducing circuits.

Sickness sleep

Sickness sleep is the increased sleep observed during infections.[100,101] This response is evolutionarily conserved, with physiological stress—arising from illness or environmental challenges—inducing sleep-like behavior in species ranging from worms and insects to rodents and humans.[100,102–106]

Emotional stress-induced sleep

A few highly specific behavioral challenges in rodents robustly promote sleep[16,56,107] (see Box 1 for more details on the protocols and Box 2 for the neural circuitry involved). Acute or chronic social defeat stress (SDS) reliably increases NREM-sleep duration and/or delta power[51,56,58,59,61,131] (Figures 1A and 1B), while REM sleep often increases following both acute and chronic SDS[51,64] (Figures 1A and 1B). Intriguingly, the winners of an SDS bout also have enhanced delta power in their NREM sleep.[60] Other examples of stress-induced REM sleep include prolonged exposure to unpredictable chronic mild stress (UCMS) (Figure 1C) and exposure to unpleasant odors, such as predator scents[27,67,132–135] (Figure 1D). Additionally, foot shock increases the likelihood of NREM sleep (Figure 1E).[68] These stress protocols can also induce arousal, depending on how the experiments are done (see Box 1 for protocols that induce arousal), but the fact that sleep can also be produced by these scenarios is intriguing.

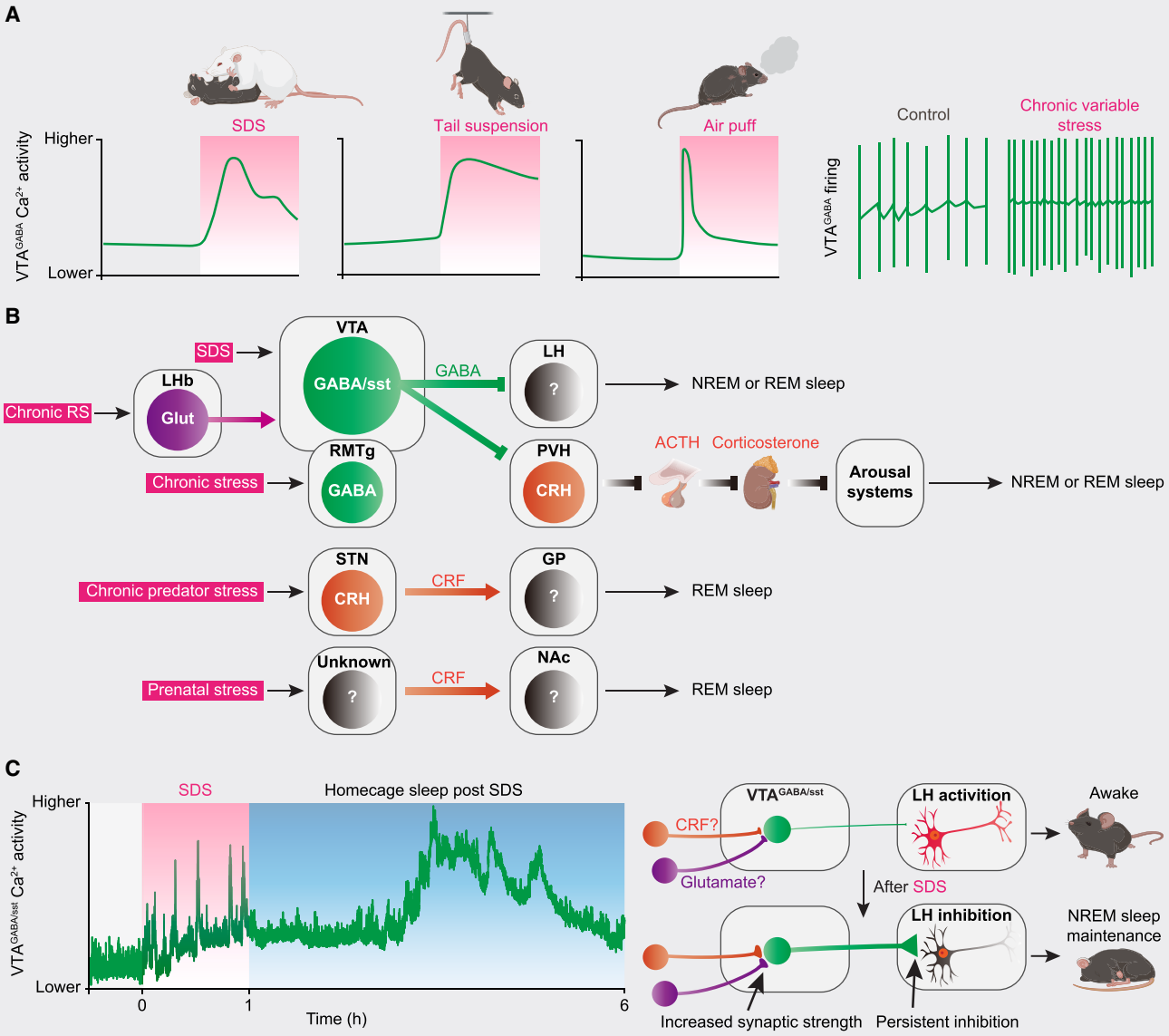
WHAT ARE THE FUNCTIONS OF SLEEP FOLLOWING STRESS?

A key hypothesis posits that animals exhibiting resilience may be those that sleep following stress exposure. The idea is that post-stress sleep allows essential housekeeping functions, enhancing recovery.[56,107] While this hypothesis is supported in animal models, it requires further validation in humans (see Box 3 for some open questions in the area). Nevertheless, a simple hypothesis is that stress of all types can produce physical exhaustion, leading to reduced latency to sleep and more prolonged sleep. However, we currently lack a clear explanation of how physical tiredness relates to sleep need.

Does sleep during sickness allow physical recovery?

Convalescence/sickness sleep seems advantageous for recovery in humans and animals post-illness.[102,136,137] The hypothesis is that this sleep supports immune responses and accelerates healing.[101,102,136,138] For instance, in the nematode worm *C. elegans*, injury-induced sleep aids cellular repair via transcriptional responses and the induction of heat shock chaperone proteins.[106,136,139] In mammals, a compelling example comes from studies on induced heart attacks[7]: in female mice, experimentally induced cardiac ischemia results in extended deep NREM sleep, lasting up to 4 to 7 days immediately following the event[7] (Figure 1F). This increased NREM sleep with elevated delta power reduces peripheral nervous system activity.[7] Rodents experiencing disrupted NREM sleep following a myocardial infarction exhibit poorer recovery outcomes, suggesting that one fundamental function of post-stress sleep may be to enforce inactivity. By attenuating autonomic nervous system activity and reducing heart rate, this enforced quiescence may facilitate physiological recovery.[7] Additionally, slow-wave sleep (SWS) may enhance left ventricular function through other mechanisms.[140]

Box 2. Circuitry linking stress and sleep



CIRCUITRY LINKING SLEEP AND SICKNESS

In mammals, there is a varied circuitry underlying how physiological stress during sickness might induce sleep. In mice, following an induced ischemic episode in cardiac muscle (i.e., a heart attack), monocytes infiltrate the brain and release a somnogen, tumor necrosis factor (TNF), in the thalamus. TNF induces NREM sleep by inhibiting thalamic relay cells and initiating thalamo-neocortical delta oscillations.[7] Sickness and inflammation frequently result in excessive sleepiness, potentially mediated by cytokines and prostaglandins that activate sleep-promoting neurons in the preoptic hypothalamic region.[109,110] Prostaglandin D2, which increases during inflammation and illness,[14] may promote sleep by activating neurons in the preoptic hypothalamic area. Another pathway that triggers sickness sleep and other sickness-related behaviors involves cytokine molecules signaling, via the vagus nerve, to the nucleus of the solitary tract (NST) in the brain stem.[111–114]

(Continued on next page)

Box 2. *Continued*

CIRCUITRY LINKING SLEEP AND EMOTIONAL STRESS. THE VTA AS A KEY HUB?

In the case of psychosocial stress-induced sleep, such as that observed after SDS in male mice, the VTA is a key integrative hub for stress signals that trigger NREM and REM sleep. VTA GABA neurons strongly promote NREM sleep when artificially activated.[51,63,115–117] These neurons are naturally activated by aversive and socially salient stimuli, receiving stress-related inputs from diverse areas[51,63,118–121] (see part A of the figure in this box), which shows the calcium photometry recordings of these neurons during SDS, tail suspension, air puff, or electrophysiological recordings (chronic variable stress, 2× repetition of foot shock, tail suspension, restraint over 6 days; redrawn from real data in Yu et al.,[51] Harris et al.,[91] and Bouarab et al.[120]). A subset of VTA^{GABA} neurons, expressing the peptide somatostatin (sst), is particularly critical for stress-induced sleep. These $VTA^{GABA/sst}$ neurons project to the lateral hypothalamus (LH) to induce sleep[51] (see part B of the figure in this box). Notably, SDS produces sustained activation of $VTA^{GABA/sst}$ cells, lasting at least 6 h, suggesting plasticity in the input pathway that supports sleep maintenance following stress (see part C of the figure in this box).[51] A closely related circuit involving the rostromedial tegmental nucleus (RMTg), a group of GABAergic neurons posterior to the main group of VTA GABA neurons, is activated by chronic stress to promote NREM sleep[78] (see part B of the figure in this box).

A critical feature of the circuit that uses $VTA^{GABA/sst}$ cells is that after stress, as well as inducing sleep, $VTA^{GABA/sst}$ cells downregulate the hypothalamic pituitary (HPA) axis by inhibiting corticotrophin-releasing hormone (CRH)-producing cells in the paraventricular hypothalamus (PVH). This inhibition reduces adrenocorticotropic hormone (ACTH) and blood corticosterone levels and mitigates arousal caused by centrally acting CRH, which otherwise activates arousal pathways[51] (see part B of the figure in this box).

Some other circuits that regulate sleep and stress likely converge on the VTA. In mice, a circuit involving glutamatergic neurons in the LHb projecting to the VTA induces REM sleep[82,122] (see part B of the figure in this box). Chronic RS induces REM sleep increases via increased activity in this circuit.[123]

CIRCUITRY REQUIRED FOR REM SLEEP ELEVATION AFTER STRESS

Beyond the VTA, other circuits contribute to REM-sleep induction in response to stress. CRH-expressing cells in the subthalamic nucleus (STN) projecting to the lateral globus pallidus (GP) are required for chronic REM elevation following chronic predator stress[27] (see part B of the figure in this box). The nucleus accumbens (NAc) may mediate lifelong increases in REM sleep resulting from prenatal stress, potentially via sustained CRH signaling[86] (see part B of the figure in this box).

CIRCUITRY THAT ALLOWS SLEEP DURING STRESS

Stressors such as cage changes provide additional insights for the circuitry that allows animals to sleep during stress. Placing mice in a cage previously occupied by another male typically induces insomnia.[124] But mice with lesioned glutamatergic neurons in the median preoptic nucleus (MnPO) of the hypothalamus sleep even less under this stress paradigm, implying that glutamatergic neurons in MnPO contribute to allowing NREM sleep during stressful situations.[124]

PERIPHERAL-BRAIN PATHWAYS CONNECTING EMOTIONAL STRESS AND SLEEP

Other endogenous factors precipitated by stress, including increased respiration, heart rate, and blood pressure, could stimulate the sleep-induction circuitry. In mice, these changes may activate neurons within the NST in the brainstem.[125] While these neurons command the reductions in heart rate and blood pressure, they also promote NREM sleep via inhibitory projections to wake-inducing adrenergic neurons.[125] Activating this circuit could, in principle, contribute to stress-induced sleep. Stress (e.g., a simple cage change for rodents) also increases body temperature by around 2°C, a phenomenon known as stress-hyperthermia.[126,127] Similarly, during SDS, body temperature rises,[128] with sleep-phase temperatures remaining slightly elevated for days after a single session. In SDS, this stress-induced hyperthermia is mediated by a prefrontal cortex-to-dorsomedial hypothalamus (PFC-DMH) pathway that warms the skin.[129] Such skin warming could be a further mechanism for potentially explaining how stress leads to sleep, since skin warmth activates, via ascending projections, nitrergic/glutamate neurons in the hypothalamic preoptic (PO) area, which results in NREM sleep.[130]

Does sleep after emotional stress increase resilience and mental recovery?

Does increased NREM or REM sleep following emotional stress contribute to recovery? One idea is that enhanced NREM sleep acts as an adaptive response to stress, fostering resilience in both losers and winners.[62] In mice, chronic stress exposure followed by sleep restriction leads to reduced social engagement (Figure 2A). Yet, when allowed post-stress sleep, a significant proportion of mice engage socially. Notably, "resilient" mice, characterized by their ability to sleep after stress, actively engage with others, while "susceptible" mice, deprived of post-stress sleep, tend to avoid social interaction[62] (Figure 2A).

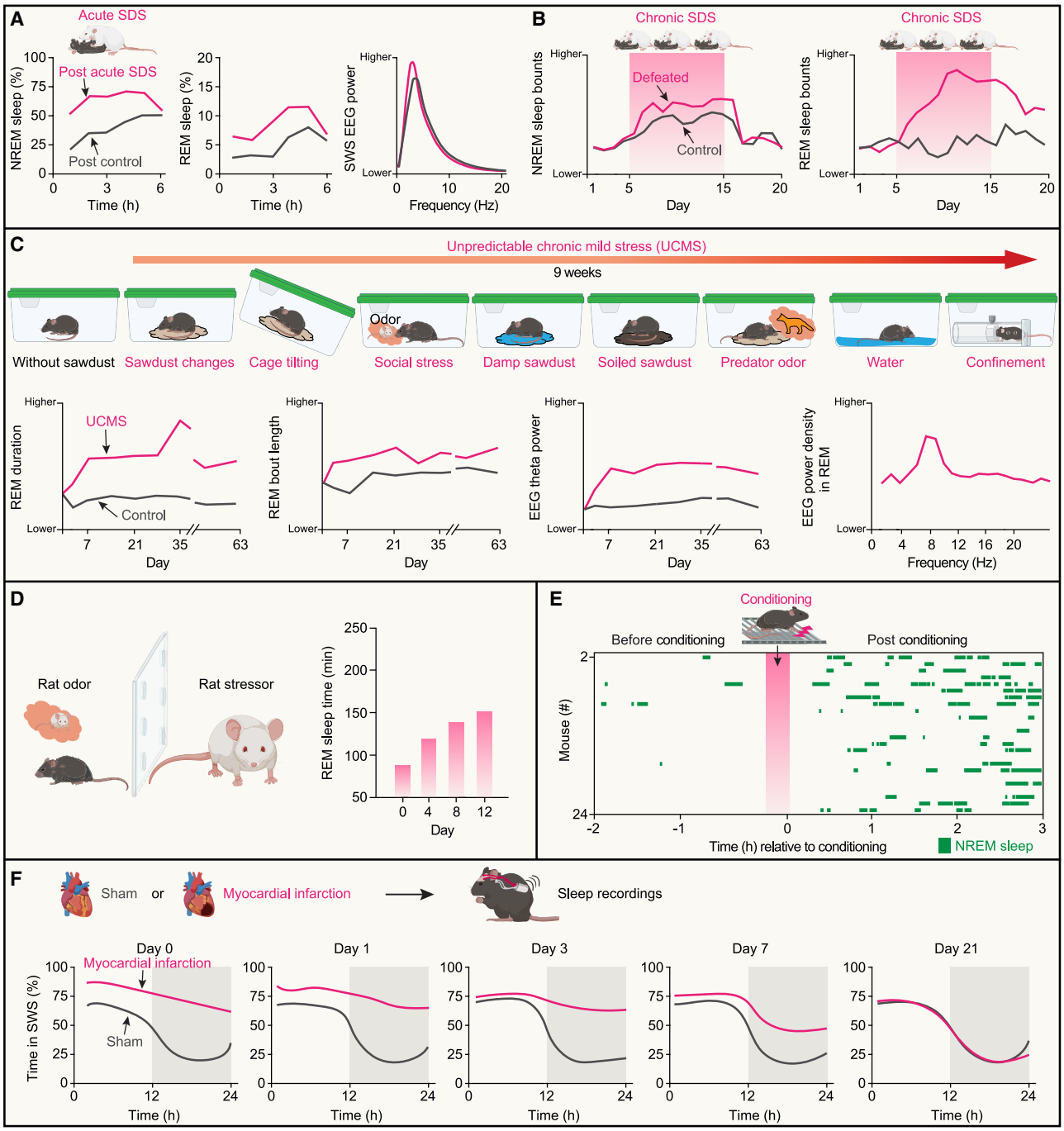


Figure 1. Stressors that induce sleep

(A) Acute social defeat stress promotes both NREM and REM sleep in defeated mice, with a marked increase in slow-wave sleep (SWS) EEG delta power during the initial 30 min of NREM sleep. This schematic is adapted from data in Yu et al.[51] and Fujii et al.[59]

(B) 10 days of social defeat stress substantially elevate the total amount and number of episodes of NREM and REM sleep in defeated mice. REM bout number remains persistently elevated for some days after the SDS period has ended. Redrawn schematically from data in Wells et al.[64]

(C) In mice that undergo an unpredictable chronic mild stress (UCMS) protocol over 9 weeks, REM sleep becomes elevated during the first week and remains persistently elevated throughout the 9-week stress period. The total duration of REM is longer, and each REM bout is longer. EEG theta power is elevated, and looking over the whole EEG power spectrum up to 20 Hz, the REM component (theta, at around 8 Hz) is selectively elevated.[67] During UCMS, NREM sleep amounts or power did not change, but NREM sleep became more fragmented (not shown). Redrawn from real data in Nollet et al.[67]

(D) Total REM-sleep time increases with the number of days a mouse is in the vicinity of a predator or exposed to predator odor. Redrawn from real data in Tseng et al.[27]

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Sleep patterns may predict a mouse's resilience or susceptibility to stress, reflected in their post-stress social behavior.[62,141] These findings imply that stress-induced sleep benefits recovery and adaptation, and poor sleep prior to distress could compromise resilience and hinder recovery.

Stress-induced NREM sleep, whether prolonged or deeper (higher delta power), may boost emotional recovery by alleviating anxiety. In mice, acute SDS produces anxiety-like behaviors, which are mitigated by a period of sleep following SDS[51,61] (Figure 2B). This sleep arises by the stress activating sleep-promoting GABA neurons in the ventral tegmental area (VTA) (see Box 2). A similar pattern is observed in aged mice with dementia-like pathology, although their sleep is more fragmented post-SDS, likely due to amyloid toxicity disrupting neural circuitry.[63] Artificially enhancing sleep in these mice via chemo-activation of VTA^{GABA} cells further reduces anxiety-like behaviors.[63] During NREM sleep, the total VTA activity, encompassing dopamine and GABA neurons, is proportional to future positive and engaged behavior[91] (Figure 2C). So it has been suggested that VTA neurons participate in offline processing to reinforce affective responses to recalled environments, ultimately influencing how animals react to future experiences, such as stress.[91]

Sleep has the potential to reduce negative impacts of stress: there is evidence in both animals and humans that sleep can both consolidate and weaken memories and allow processing of emotions.[11,142–148] One hypothesis is that REM sleep may allow stress recovery by boosting emotional resilience.[67,143–147,149,150] In mice, this could work by facilitating the erasure of poignant, emotionally loaded, or traumatic memories.[146,150–152] A circuit that incorporates the glutamate neurons in the lateral habenula (LHb) projecting to the VTA induces REM sleep.[122] Chronic inhibition of the LHb over several days depletes REM sleep, leading to heightened anxiety and increased sensitivity to aversive stimuli.[122] Another example is fear extinction (losing the association between an auditory tone and foot shock), whereby the excitability of infralimbic (prefrontal) neocortical pyramidal neurons is specifically enhanced during REM sleep.[152] Strikingly, this REM-dependent process must occur within the first few hours post-learning to promote fear extinction.[152] The regulation of this stress-induced REM sleep, or more specifically, how the pyramidal cell excitability is regulated post stress, requires GABA interneurons.[151]

Why do some stressors induce NREM and others REM sleep?

Beyond the general question of why stress induces sleep, it remains puzzling why, in animal models, some stressors promote NREM sleep, others trigger REM sleep, and some induce a mix of both (Figure 1). Addressing this will require understanding the specific functions of these sleep stages (Box 3; Figure 3). Although some studies find that REM sleep is needed for emotional memory consolidation and/or forgetting emotional stimuli,[145] other work finds that SWS REM together account for emotional memory consolidation.[148]

DOES EMOTIONAL STRESS-INDUCED SLEEP OCCUR IN HUMANS?

It is assumed that most emotional stressors promote insomnia in humans.[33,36] However, working outside laboratory settings poses challenges, particularly due to the difficulty in clearly defining and measuring "daily life stress."[36] There are also many "hidden variables," such as circadian timing and ethological context of the stressor, as well as differences in individual coping strategies in response to the stress that could confound interpretation of the results.[153] Thus, identical stressors can produce different effects in different people.[153] Such hidden variables likely explain why in an earlier meta-review of the effects of psychosocial stress on sleep in humans, it was concluded that although such stress tended to produce insomnia, there was much inconsistency in the literature, and stress needed to be more precisely defined "in terms of duration and severity and to measure its impacts on sleep in populations that differ in terms of age, comorbid illness, gender, and so forth.[36] Without such fine-grained analyses, it is difficult to draw definitive conclusions."[36]

Recent studies have leveraged virtual reality (VR) to investigate the effects of pre-sleep social stress on sleep quality (Figure 2D). In the evening, healthy participants were exposed to a VR-based public speaking scenario designed to simulate real-life social stress and induce acute stress immediately before sleep.[90] The control condition involved a passive listening task in VR. The public speaking task elicited both a subjective perception of stress and a transient physiological stress response. Compared with controls, participants who underwent the public speaking task exhibited a prolonged duration of SWS during the initial sleep period, with the most pronounced effects occurring in the early stages of sleep (Figure 2D).[90]

In another approach, using trauma movies, increasing the amount of sleep in volunteers after a simulated/analog trauma (see Box 2) correlated with a reduction in subsequent "trauma" memories[92,154,155] (Figure 2E). According to one study, nappers had reduced intrusive memories, but only when the sleep included REM.[92] By contrast, another study reported that a 1-h nap, even without REM sleep, reduced intrusive memories by approximately 50% following a trauma-film paradigm.[156] Meta-reviews have concluded that sleep after synthetic trauma reduces the frequency of intrusive memories, although the observed effects are modest.[157–159]

Real-life trauma presents a more complex picture, and hidden variables are in full play. Patients admitted to emergency clinics after traumatic events displayed no consistent sleep patterns.[160] It was actually those patients with *unchanged* amounts of (self-reported) sleep in the subsequent weeks who fared better in having lower frequencies of intrusive memories.[160] Clearly, these results could be greatly confounded by what went on in the emergency room post trauma. Also, for studies lacking electroencephalographic (EEG) data, potential changes in sleep

(E) Fear conditioning (electric foot shock) elevates NREM sleep after the shock. Raster plots of NREM sleep scoring of 24 individual mice before and after foot shock. Illustration redrawn and adapted from Subramaniyan et al.[68]
(F) Sustained increases in robust NREM sleep were observed over a 24-h period, lasting up to 7 days following myocardial infarction associated with "sickness." This schematic is adapted from data in Huynh et al.[7]

Box 3. Some key unsettled questions that could deepen our understanding of how stress influences sleep and vice versa

CAN THE SELECTION OF STRESSORS IN ANIMAL MODELS BE IMPROVED?

Animal models employing stressors to simulate human stress offer insights but face limitations due to species differences. How stress influences sleep-wake states and behavior in animals depends on the experimental design, underscoring the need to avoid an arbitrary selection of stressors. A single stressor may oversimplify the complex nature of human stress responses. To enhance the translational value of these models, it will be desirable to utilize diverse or combined stress paradigms. Incorporating both psychological and physical stressors will be critical to creating more comprehensive models that better reflect the interplay of these factors in humans (Figure 3A). Algorithms such as DeepLabCut, which reveals and classifies the intricacies of animal movements in naturalistic settings,[108] could refine our understanding of how specific stressor features evoke sleep. These methods could help delineate the sequential or simultaneous functioning of circuitry that initiates sleep after stress.

WHAT ARE THE NEUROBIOLOGICAL MECHANISMS LINKING STRESS TO SLEEP INDUCTION OR, CONVERSELY, TO SLEEP DISRUPTION?

We need a complete picture of the circuitry and associated changes in neuromodulator transmitters. Identifying the neural pathways that link stress to disrupted or enhanced sleep could help target more effective therapeutic interventions for sleep disorders tied to stress (Figure 3B).

IN ANIMALS, WHY DO THE TIMING AND INTENSITY OF STRESS DIFFERENTIALLY AFFECT NREM AND REM SLEEP? HOW DOES THE INDUCTION OR DISRUPTION OF SPECIFIC STAGES OF SLEEP (E.G., NREM AND REM) DURING STRESS CONTRIBUTE TO BOTH SHORT-TERM AND LONG-TERM HEALTH OUTCOMES (E.G., IMMUNE FUNCTION, CARDIOVASCULAR HEALTH, AND EMOTIONAL REGULATION)?

This research could lead to more targeted sleep interventions that focus on improving specific stages of sleep, which may be more effective at mitigating the effects of stress, e.g., high delta power NREM sleep benefits heart recovery[7] (Figure 3B).

HOW DOES STRESS IMPACT PERIPHERAL-TO-BRAIN PATHWAYS IN SLEEP REGULATION?

Stress, whether psychosocial or physiological, profoundly affects the endocrine, immune, and autonomic systems, influencing brain function and sleep-wake regulation, particularly under pathological conditions, through mechanisms that remain poorly understood. Investigating these peripheral-to-brain pathways in both health and disease is essential for identifying novel therapeutic strategies. Such efforts will require interdisciplinary approaches (Figures 3B and 3C).

DOES A PERSON'S NATURAL SLEEP-WAKE CYCLE (CHRONOTYPE, MORNING VERSUS EVENING PERSON) INFLUENCE HOW THEY RESPOND TO STRESS IN TERMS OF SLEEP DISRUPTION/INDUCTION, AND VICE VERSA?

Interventions could be tailored to an individual's biological rhythm, potentially improving both sleep and stress management (Figure 3D).

CAN IMPROVING SLEEP QUALITY (THROUGH SLEEP HYGIENE, COGNITIVE BEHAVIORAL THERAPY) BE USED AS AN INTERVENTION FOR STRESS MANAGEMENT?

For instance, does sleep improve the ability to cope effectively with stress and trauma (e.g., natural disasters, personal loss, or workplace stress)? Conversely, does poor sleep following stress directly contribute to the development of anxiety, depression, or PTSD? If better sleep can reduce stress levels or improve stress resilience, sleep-based interventions could become an integral part of managing chronic stress and preventing stress-related disorders, with sleep interventions playing a key role in reducing the long-term psychological impact of traumatic events (Figures 3E and 3F).

architecture in response to stressors, such as increases in NREM depth or sleep stage shifts, may have been overlooked.

ARE THERE DOWNSIDES TO STRESS-INDUCED SLEEP?

So far, we have assumed that stress-induced increases in sleep are beneficial and adaptive. Contrary to the view that stress-induced sleep promotes recovery, there is also evidence suggesting that avoiding sleep immediately after stress may, in some cases, be beneficial. A starting point is the striking observation that, despite the physiological necessity of sleep, acute sleep deprivation of people living with severe depression can transiently alleviate their depressive symptoms.[161,162] In mice, this antidepressant effect is linked to enhanced dopamine release into the prefrontal cortex during the extended wake period.[163] Similarly, by analogy with the positive effect of sleep deprivation on lifting depression, acute sleep deprivation after traumatic events may be beneficial.[164] When male volunteers

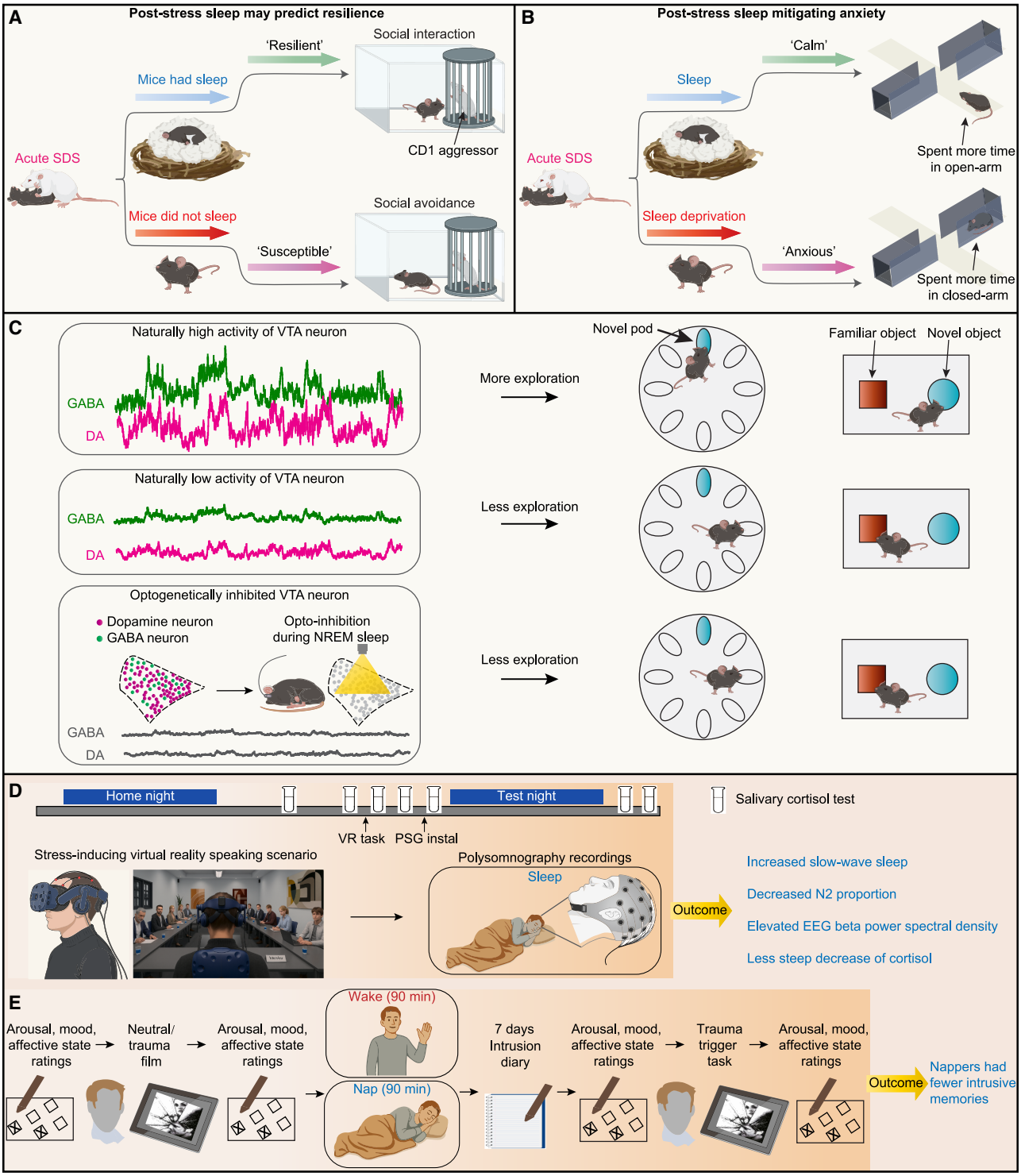

Figure 2. Sleep after stress reduces anxiety and is associated with resilience and engaged behavior

(A) C57BL/6J mice that endured multiple days of social defeat stress followed by sleep restriction have reduced social activity and do not go near other mice. But if they can sleep after the social defeat rounds, then they will approach (caged and novel) CD1 aggressor mice. Redrawn from data and concepts in Bush et al.[62]

(B) Sleep following single bouts of social defeat stress (4 sessions in 1 h) is associated with a reduction of anxiety, as indicated by the performance of mice in the open-arm maze. If mice are sleep deprived after social defeat stress, they are anxious. (Mice that venture out less into the open arms are assumed to be anxious). Redrawn from data and concepts in Yu et al.[51] and Feng et al.[61] SD, sleep deprivation.

(legend continued on next page)

were given emotionally laden texts to read, subjects that had a 3-h sleep after the tests could still recall these unpleasant texts 4 years afterward, whereas those that did not sleep had less recall.[165] This led to the hypothesis that sleep deprivation immediately after trauma might disrupt memory consolidation, preventing the formation of traumatic memories.[165] Rodent studies provide further support.[166,167] Post-stress sleep deprivation reduces aversive memory formation and diminishes stress responses in subsequent situations.[168] While these findings are intriguing, there is considerable scope for more studies with real-world human scenarios to fully understand the implications. It is unclear how these results align with or challenge the concept of stress-induced sleep as an adaptive response (see Box 3).

INCREASED REM SLEEP DURING DEPRESSION: ADAPTIVE OR MALADAPTIVE?

The question of whether increased REM sleep during depression is beneficial or detrimental remains unresolved. This debate mirrors the broader ambiguity around whether sleep after stress is advantageous. It is well established that individuals with severe depression often exhibit prolonged REM sleep and reduced REM latency.[169–171] Yet common antidepressants (tricyclic antidepressants, selective serotonin, and serotonin-noradrenaline re-uptake inhibitors) suppress REM sleep.[170] Is this suppression helpful or harmful? Some argue that the enhanced REM sleep reflects and exacerbates the depressive state. Conversely, we would suggest that the REM sleep may serve as an adaptive, positive response. From the animal experiments outlined above, stress-induced REM sleep contributes to processes such as fear extinction,[152] and we would posit that removing REM sleep in humans living with depression is not desirable. Yet some investigators argue that selective REM depletion could be a specific treatment for depressive patients.[172] For example, chemogenetic inhibition of LHb glutamatergic neurons projecting to the VTA, which induces REM sleep,[82,122] reduces depressive-like behaviors in mice (as assessed by the forced swim test—mice with less REM struggle more[82]). This finding could suggest that increased REM sleep is maladaptive, contributing to depressive symptoms. However, chronic inhibition of the LHb, leading to REM sleep depletion, heightens anxiety and sensitivity to aversive stimuli (mice venture less into open areas and startle more in the presence of a looming shadow).[122] It is important to note that these studies face limitations, particularly regarding causality. While REM sleep changes are observed, they may not directly drive behavioral outcomes. The depressive-like behaviors could instead arise from activity in other circuits downstream of LHb projections unrelated to REM sleep. Animal models are useful to understand pathophysiological features of depression but possess inherent limitations. REM sleep in rodents might not serve the exact same purposes/functions as in humans. Bearing in mind this postulate, REM-sleep alteration might be both beneficial and detrimental depending on the phylogenetic context.

CONCLUDING REMARKS

In 1984, Lazarus and Folkman put forward the idea that "while stress is an inevitable aspect of the human condition, it is coping that makes the big difference in adaptational outcome."[98] Does post-stress sleep enable effective coping (see key questions in Box 3 and Figures 3D–3F)? If it does, this coping enabled by sleep could include physical as well as mental recovery. The physical elements of stress-induced sleep could include cellular repair, and the mental aspects would include emotional regulation and increased cognitive function. In rodents, certain emotional and physiological stressors induce sleep through specific neural circuits that, when appropriately activated, allow sleep to emerge after stress. Evidence suggests that rodents that are resilient to stress may be those that sleep following exposure to stress, a pattern also observed in sickness-induced sleep. The existence in rodents of dedicated circuits that promote sleep following stress, in other words, the capability of a hard-wired response (see Box 2), suggests that the elements of this system could also be present in humans. Can we harness this capacity for helping humans deal with emotional aspects of sleep? Large-scale human studies are needed to clarify whether post-stress sleep is beneficial or harmful for mental health. It is likely that animals, while experiencing suffering, do not engage in reflective thought about its meaning. Instead, the inherently physiological and potentially restorative circuit-driven mechanisms of sleep appear to take precedence following stress. By contrast, humans often struggle to achieve post-stress sleep due to intrusive thoughts and worry, which may hinder any potentially restorative process. Nevertheless, we suggest that for humans, post-stress sleep has the capacity to build resilience. Understanding the underlying mechanisms and how this process can be enhanced offers an opportunity to develop strategies for better stress management and recovery.

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AUTHOR CONTRIBUTIONS

X.Y. created the figures. All authors—X.Y., M.N., N.P.F., and W.W.—took part in conceiving, writing, and revising the manuscript.

(C) Activity of VTA GABA neurons in NREM sleep shapes the next day's exploratory behavior. If NREM active VTA GABA neurons are optogenetically inhibited selectively during NREM sleep, mice show less exploratory behavior on a Barnes maze, where they learn to identify the correct escape hole in a brightly lit arena. Mice with NREM sleep-inhibited VTA GABA neurons preferred familiar behaviors rather than novelty. Redrawn from conclusions and concepts in Harris et al.[91]
(D) In human studies, a virtual reality (VR) experiment demonstrated that exposure to psychosocial stress, specifically a public speaking task in the evening, was associated with an extended duration of slow-wave sleep (SWS) during the immediate subsequent sleep period. Adapted and redrawn from Hein et al.[90]
(E) For experiments with human subjects, movies can help probe if sleep immediately after viewing a film containing traumatic content is beneficial for reducing the number of intrusive memories. Adapted and redrawn from Wilhelm et al.[92]

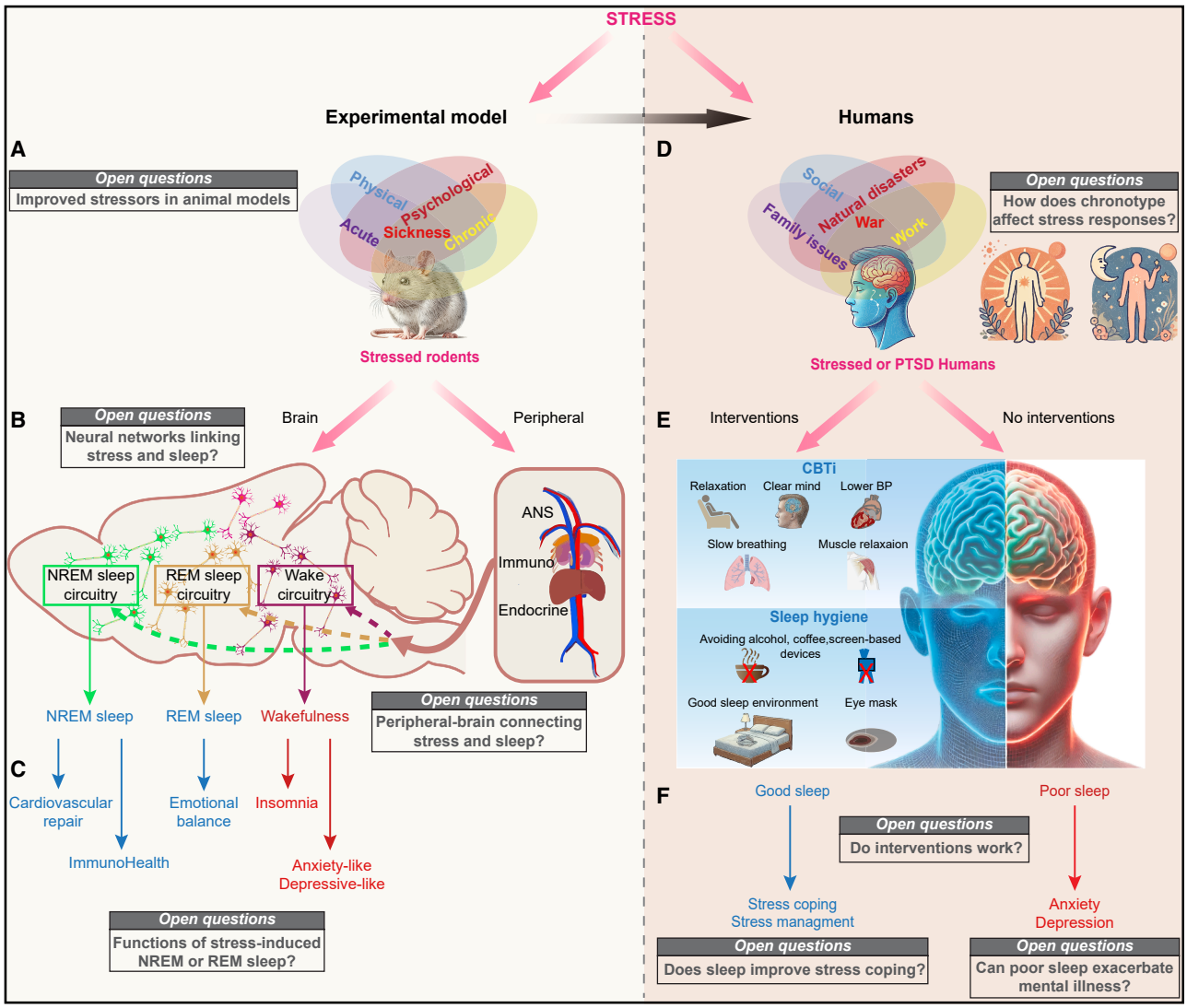

Figure 3. Open questions on stress-induced sleep from rodents to humans

(A and B) Perspectives for rodent research.

(A) Implementation of diverse stress paradigms: future research should incorporate diverse or combined stress paradigms to address both physical (e.g., injury and hyperthermia) and psychological (e.g., social defeat and unpredictability) stressors. This approach will offer a more comprehensive understanding of how various stress modalities influence sleep architecture, brain states, and behavioral outcomes.

(B) Refining circuitry linking stress to brain states: the current understanding of brain-wide and peripheral-to-brain stress architecture remains incomplete. Mapping the interactions between stress-related regions and sleep-wake systems, as well as peripheral-to-brain pathways, will help identify critical hubs and circuits mediating stress responses. Advanced tools such as large-scale imaging, neural tracing, and functional manipulations are essential to elucidate these complex networks. ANS, autonomic nervous system.

(C) Elucidating post-stress sleep functions: the functional significance of post-stress NREM and REM sleep remains poorly understood. NREM sleep may promote recovery by reducing autonomic activity and supporting physiological repair, while REM sleep may enhance emotional resilience through processes such as fear extinction and memory reconsolidation. Future studies should focus on delineating the distinct contributions of these sleep stages to stress recovery using integrative methods, including EEG, behavioral assessments, and targeted circuit manipulations.

(D and E) Perspectives for human research.

(D) The role of chronotype in stress and sleep regulation: an individual's natural sleep-wake pattern, or chronotype, may influence their vulnerability to stress-induced sleep disturbances or sleep induction. Similarly, stress itself could alter an individual's biological rhythm, disrupting sleep patterns. Investigating these interactions could help develop personalized interventions aligned with biological rhythms, optimizing sleep quality and stress management outcomes.

(E) Targeted interventions to alleviate stress and improve sleep: can enhancing sleep quality serve as a viable intervention for stress? Approaches such as cognitive behavioral therapy for insomnia, improved sleep hygiene, or other evidence-based strategies may improve stress coping mechanisms. Understanding whether better sleep reduces vulnerability to stress-related conditions, including anxiety, depression, or post-traumatic stress disorder (PTSD), remains critical. Conversely, poor sleep following stress may exacerbate these conditions. Defining individualized treatment protocols will be essential for maximizing therapeutic benefits.

(F) Sleep as a tool for enhancing stress resilience: if improving sleep quality can mitigate stress and enhance resilience, sleep interventions could become integral to managing chronic stress and preventing stress-related disorders. By prioritizing sleep health, these approaches may significantly reduce the long-term emotional and psychological burden of traumatic or chronic stress.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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