Improving Sleep to Improve Stress Resilience

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Abstract

Purpose of Review The neuroendocrine stress response is a natural process of our body which, however, might become toxic if not properly turned on and off. Resilience is the ability to adapt to adverse situations and, particularly, to cope with uncontrolled stress. Resilience and stress are two opposite faces of the same coin, and both are deeply linked to sleep: low resilience means higher stress and, through that, more sleep disorders. The aim of the present paper is to review the complex relationship between these actors and to highlight the possible positive role of good sleep in contrasting chronic stress situations.
Recent Findings Promotion of cognitive-behavioral therapy for insomnia patients improves sleep quality and, through that, produces lower general stress, lower depressive symptom severity, and better global health.
Summary Sleep is a modifiable behavior and, according to recent studies, its improvement might enhance resilience and, in turn, reduce stress.

Keywords Sleep · Stress · Resilience · Insomnia · dCBT-I

Introduction

Stress is an automatic response of our body implemented to face physical or psychological adversities with the purpose of restoring homeostasis. To keep constant our internal ambient (homeostasis), the stress response modulates many physiological functions, acting from the molecular (gene transcription regulation) to the more integrated (brain activity and behavior) levels. The ability of an individual to adapt to stressful situations is called resilience. Therefore, the stress response is a natural process of our body, and in this way, it should not be considered toxic but rather crucial for survival. In this respect, the stress response is an active mechanism by which organisms, by prediction and feedforward mechanisms, adapt to environmental changes or potential threats in order to maintain homeostasis and promote survival [1]. However, when allostatic adaptations become chronic, are not turned off at the end of the stressing situation, or are improperly turned on, they become potentially toxic and are usually identified as allostatic load or overload [1].

The physiological response to stress involves both the endocrine and the nervous system (Fig. 1a) with massive release of hormones and neurotransmitters. It is generally accepted that the neuroendocrine stress response also entails stimulation of wakefulness and inhibition/fragmentation of sleep states [2]. In the last few years, however, several studies demonstrated that the relationship between sleep and stress responses is bidirectional [3]. Sleep disorders, which are increasingly prevalent in the general population, are associated with significant adverse behavioral and health consequences. Indeed, if on one hand good sleepers show reduced stress-related neuroendocrine activation, on the other hand, insomnia patients suffer from hyperactivation of their stress responses. The hyperactivity of the stress system contributes to worsening their hypnic phenotype, reinforcing the hyperarousal status (Fig. 1b).

Along this introduction, we will describe the neuro-endocrine stress response, the different classes of stress which we might face during lifetime, the individual predisposition to stress resilience and susceptibility, and the effects of stress on the wake-sleep cycle. Then, we will conduct a narrative review of the most recent scientific literature on the relationship between sleep, stress, and resilience particularly focusing on the evidence supporting the hypothesis that good sleep improves stress resilience.

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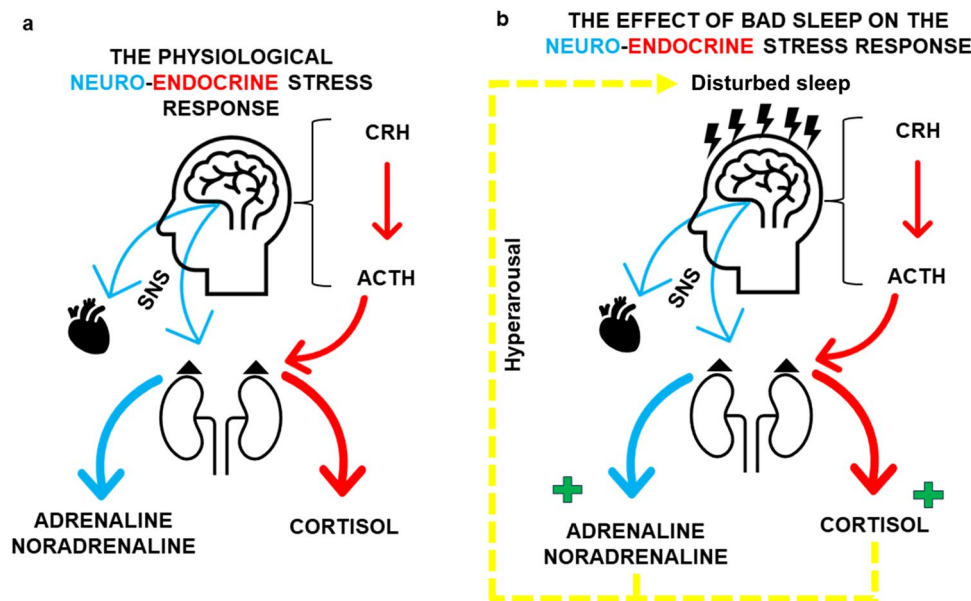   Piazza di Porta San Donato 2, 40126 Bologna, Italy

Fig. 1 The neuro-endocrine stress response. **a** Schematic representation of the physiological response to stress which relies on the activation of the hypothalamic-pituitary-adrenal (HPA, in red) axis and of the sympathetic nervous system (SNS, in blue). The chemical/hormonal mediators of the HPA axis are the corticotropin-releasing hormone (CRH) which is produced by the hypothalamus and leads to pituitary release of adrenocorticotropin (ACTH). ACTH, in turn, produces the release of cortisol from the adrenal glands. On the other hand, SNS promotes the fight or flight response through increased heart rate and blood pressure, bronchodilation, pupil dilation, adrenaline/noradrenaline release from adrenal glands, and so on. **b** Disturbed sleep may alter the normal HPA axis functioning and the ANS responses leading to increased levels of cortisol, ACTH, adrenaline, and noradrenaline which, in turns, induce a hyperarousal state (yellow arrow)

The Neuro-Endocrine Stress Response

The physiological response to stress relies on the activation of two major pathways: the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system (ANS) which, respectively, entail the production of several hormones and the activation of the fight or flight response (Fig. 1a).

The ANS has three branches, the sympathetic (SNS), the parasympathetic (PNS), and the enteric nervous system (the latter will not be further discussed being primarily involved in digestive control). The principal neurotransmitters of the ANS are noradrenaline and adrenaline for the SNS and acetylcholine for the PNS. The opposed actions of the SNS and PNS are usually coordinated and balanced to maintain body homeostasis. During stressful situations, however, the SNS may overwhelm the PNS to promote the fight or flight response through increased heart rate and blood pressure, bronchodilation, pupil dilation, adrenaline/noradrenaline release from adrenal glands, and so on. Neurons in the paraventricular nucleus (PVN) of the hypothalamus play a key role in the activation of the SNS and of HPA axis. Indeed, the PVN neurons can be divided into three main groups: (i) the preautonomic neurons; (ii) the magnocellular neuroendocrine neurons, responsible for the secretion of vasopressin and oxytocin; and (iii) the parvocellular neuroendocrine neurons that secrete several hormones to the anterior pituitary lobe. Among the latter, corticotropin-releasing hormone (CRH) neurons lead to pituitary release of adrenocorticotropin (ACTH) and, in turn, of glucocorticoids from the adrenal glands [4]. This HPA axis represents the most important hormonal pathway activated by stressful events (Fig. 1) and it has circadian rhythmicity with the highest plasma corticosteroid levels before awakening (i.e., cortisol awakening response) and lowest before sleep. High levels of glucocorticoids increase blood glucose, lipolysis, and glucagon while inhibit insulin release, B cell antibody production, and neutrophil migration during inflammation. PVN preautonomic neurons also influence the ANS activity projecting to noradrenergic centers in the brainstem (such as the locus coeruleus) and to intermediolateral cell column of the spinal cord. The locus coeruleus increases sympathetic activity through the activation of α1-adrenoceptors on preganglionic sympathetic neurons [5] and reduces parasympathetic activity through the activation of α2-adrenoceptors on preganglionic parasympathetic neurons [6].

In the setting of a stress response, the endocrine and nervous systems exert control over each other's activity, with the HPA system being slower and more persistent in its actions involving hormones secreted by the adrenals [7]. While short periods of controllable stress may be beneficial to face environmental perturbations, a lack of control can produce

distress enhancing vulnerability to several diseases. For this reason, negative feedback control mechanisms of the HPA axis are crucial [2, 8]. Corticosteroids inhibit the HPA axis activity both at the hypothalamic and pituitary level reducing, respectively, the release of CRH and ACTH. Corticosterone binds to two types of receptors, the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR). GRs are widely expressed in the brain, particularly in the hypothalamic CRH neurons and pituitary corticotropes, while MRs are typically found in dentate gyrus, CA2 and CA1 of the hippocampus, lateral septum, and central amygdala [9]. The hippocampus is critical in the regulation of HPA axis activity inhibiting hypothalamic CRH release [8]. Electrophysiological and behavioral studies suggest that GR and MR may exert different, and even functionally antagonistic, effects. For instance, in the hippocampus, MR activation maintains excitability and regulates behavioral reactivity and response selection, while GR occupancy suppresses excitability and facilitates storage of information [10]. On the other hand, MR and GR actions on HPA axis regulation appear to be synergistic. Hippocampal MR is important in controlling the basal inhibitory tone along the HPA axis and at the onset of the stress response. This effect of cortisol via MR is modulated by GR, which facilitates the termination of the physiological stress response [11]. The hippocampal MR and GR also play distinct roles in the control of SNS outflow to stressful events [12]. Altogether, this dual binding receptor system regulates the physiological (endocrine and autonomic) responses under baseline and stress conditions, maintaining homeostasis and facilitating long-term adaptation, thus safeguarding resilience of the organism [9].

Different Types of Stress at Different Ages of Life

Numerous studies conducted on both animals and humans have shown that the effects exerted by stress vary with the duration of exposure [13]. Short-term (acute) and long-term (chronic) stress activate different regulatory mechanisms involving the HPA axis, as well as cortisol metabolism. Acute stress produces an immediate and nonspecific behavioral response (followed only later by more targeted behaviors for different types of stress). This acute behavioral response is followed by activation of the SNS within seconds, and then by recruitment of the HPA axis, with a peak of cortisol between 15 and 20 min after the onset of stress [14]. Beside early, non-genomic actions, glucocorticoids also exert slower long-term anti-inflammatory and immunosuppressive effects by modulating pro-inflammatory transcription factors [15]. In response to chronic stress, the increase in cortisol levels remains high over time, due to a reduction in both its metabolism and the sensitivity of the feedback mechanisms that regulate its

release. In chronic stress, the release of arginine vasopressin (AVP) from the PVN is important in determining the increase in cortisol release: indeed, AVP stimulates the synthesis of pituitary ACTH thus modulating the release of glucocorticoids from the adrenal gland. For example, repeated restraint stress in rats continues to induce elevated expression of AVP but not CRH [16].

As research conducted in recent years has shown with increasing clarity, the effects of stress on the neuroendocrine profile can persist for a very long time, even after the cessation of exposure to the environmental factors that produced it [17]. Exposure to adverse events during the perinatal period, a phase of life characterized by a very high level of neuroplasticity, can leave a permanent imprint on physiological systems, triggering a maladaptive program that alters stress resilience mechanisms during the entire life span. Perinatal stress can determine a neuroendocrine reprogramming, generating an increased susceptibility of the individual to the development of different pathologies, such as cardiovascular diseases, metabolic syndrome, cognitive disorders, and affective disorders [18] in adulthood. These long-term and stable phenotypic changes are linked to persistent alterations in gene function: environmental factors intervening in the perinatal period can modify individual epigenetic profile, producing long-term changes in gene expression in the brain and in other organs [19]. Epigenetic mechanisms can act both upstream and downstream of transcription, but the main regulators of gene state of activity are DNA methylation and its hydroxymethylation [17]. Downstream of transcription, gene function can be modified by non-coding RNAs and micro-RNAs, which affect mRNA stability and may arrest translation [20].

Studies conducted in recent years on the long-term effects of perinatal stress strongly suggest a role of epigenetic modulation of CRH, GR, and MR expression in HPA structures, and particularly in the hippocampus, produced in fetuses or newborns by the increase in cortisol levels [2, 21]. For example, it has been shown that poor maternal care was responsible for the hypermethylation of the GR promoter and the consequent decrease in the number of hippocampal GRs in the offspring [22]. Since the hippocampus plays a key role in regulating HPA axis negative feedback, a low number of GR in this area reduces hippocampal inhibition of the HPA axis, determining a long-term dysregulation of cortisol release, with high corticosteroid levels in adults. Interestingly, epigenetic modifications of gene expression are potentially reversible. Indeed, rescue experiments have shown that in perinatally stressed adult rats the increased corticosterone levels normalize after demethylation of the hippocampal GR promoter [22, 23].

Resilience and Susceptibility to Stress

Stressful stimuli that have deleterious effects in several subjects do not act as stressors in many others, capable of maintaining normal physiological and psychological profiles, and of avoiding negative consequences [24]. It is precisely the observation of individual differences in reactivity to stress that led to the concept of resilience as "the process and outcome of successfully adapting to difficult or challenging life experiences" [25]. In recent years, scientific research has tried to identify the characteristics that make individuals resilient, also using animal models. As in humans, chronic stress in animals produces anxiety-like behaviors only in a sub-population of exposed subjects (see [24] for a review). Resilient animals, while not symptom-free, exhibit resistance to several maladaptive sequelae of chronic stress. The use of animal models allowed to identify some of the neural and molecular mechanisms of resilience. A role for the medial prefrontal cortex (and in particular for the prefrontal dopaminergic system) and other structures of the limbic system and midbrain has emerged [26, 27]. Many different pathways involved in stress response have been identified. Between these, there are DAF-16, a *Caenorhabditis elegans* gene, homolog of mammals Fox genes, encoding transcription factors with roles in apoptosis, DNA repair, metabolism, stress and immune responses, and the cytoplasmic unfolded protein response, a mechanism activated by acute stresses (for a complete review see [28]). However, many aspects still need to be clarified: for example, it is not known whether there is a specificity of regions involved linked to the type of stressor, or to the timing of the response (initial vs long-lasting). Of particular interest is that only some of the molecular and cellular mechanisms identified in resilience are the same as those in stress susceptibility, operating in the opposite direction, while others play unique roles in stress resilience [29]. This suggests that resilience is not simply due to the absence of maladaptive responses to stress but rather to active and adaptive processes. The main factors implicated in the differences between subjects in their cooperative capacities include the genotype, the social support that individuals can benefit from, and the experiences of the perinatal period [30].

Another interesting aspect is that, in addition to decreasing the immediate deleterious effects of stressful stimuli, resilience to stress is positively correlated with lifespan [28]. Studies on animal models have shown that mutations associated with longer lifespan are also associated with greater resistance to stress, and long-lived mutants exhibit upregulation of genes involved in multiple stress response pathways [31]. The relationship between stress resistance and aging is also supported by the observation that resistance to multiple external stressors decreases with age [32], at least in part due to a genetically programmed downregulation of stress pathways [33].

Effects of Stress on Wake-Sleep Cycle

Several studies have suggested that stress can alter wake-sleep patterns, both in humans and animals. One possible way by which stressful events can influence sleep is the activation of HPA axis (Fig. 1b). Thus, in the following paragraphs we will examine the effects of HPA axis mediators on wake-sleep cycle regulation [34].

CRH

Secretion of CRH from the PVN of the hypothalamus results in peak during arousal and wakefulness. CRH is present in many other brain regions such as in limbic system, sympathetic brainstem and spinal cord, and interneurons of cortex [35], indicating its role as neuromodulator even in the absence of stressors [36]. Many studies hypothesize that the regulatory influence of CRH on sleep and waking is mainly due to its central effects [37]. Indeed, central administration of CRH in rats, rabbits, humans, and mice increased wakefulness [37–39]. Rat strains with reduced synthesis and secretion of CRH showed reduced time spent awake and increased time spent in non-rapid-eye-movement (NREM) sleep than controls [40]. Moreover, the interfering with the binding of CRH to its receptors has been demonstrated to reduce wakefulness [39]. The administration of two different CRH receptor antagonists reduced the percentage of wakefulness when injecting during the activity (dark) period, while they exert no effect during the resting (light) period. These experiments suggested a role of CRH only in the control of physiological periods of wakefulness [41, 42]. Another study, however, failed to replicate these results using a different CRH antagonist [43]. In the same study, the investigators reported a complete abolishment of basal rapid-eye-movement (REM) sleep and a reduction in the amount of REM sleep rebound after immobilization stress and sleep deprivation [43]. Accordingly, mice overexpressing CRH showed, compared to controls, higher percentage of basal REM sleep and elevated levels of REM sleep after 6 h of sleep deprivation [44].

Studies performed in humans yielded contrasting results. Born and colleagues suggested that the peripheric infusion of CRH had no intrinsic effects on sleep regulation [38]. Later, other studies demonstrated that after pulsatile intravenous administration of CRH, subjects showed a decrease of stage 3 of NREM sleep, an increase of intermittent wakefulness, and an increase of the time spent in REM sleep during the first third of the night [45]. These effects were more evident in women than in men. However, other studies showed that the infusion of an antagonist for the CRH

receptor-1 after 4 weeks increased the amount of NREM sleep with a decrease in the number of awakenings and REM sleep density [46].

In conclusion, the role of CRH as waking-promoter and NREM sleep-inhibitor molecule is widely accepted; on the other hand, more studies are needed to elucidate the effects of CRH on REM sleep in the different species.

ACTH

ACTH is considered a waking-promoter molecule since its infusion produced a significant increase in sleep latency, a decrease in NREM sleep time, and an increase in wakefulness time [47] in rats. Accordingly, ACTH infusion in cats decreased the number and duration of REM sleep episodes [48]. In human subjects, the pulsatile intravenous infusion of an ACTH analog caused a decrease in NREM sleep whereas intermittent wakefulness and sleep latency were increased in the first third of the sleep period [49]. These results account for a role of ACTH in increasing wakefulness at the expense of NREM sleep in both humans and animals; the effects on REM sleep are still incompletely understood.

Cortisol

Cortisol (or corticosterone in rodents) is released by the adrenal cortex in response to the activation of the HPA axis. In adrenalectomized rats a decrease in the amount of NREM sleep was induced by the injection of supraphysiological doses of corticosterone [50]. However, another study demonstrated that the administration of three increasing doses of corticosterone in rats induced an initial enhancement of wakefulness at the expense of NREM sleep. This effect was evident within the first hour for all the doses but lasted until the third hour only after the higher dose. REM sleep was not affected by corticosterone administration at none of the doses delivered [34]. Recently, it has been demonstrated that the chronic intraperitoneal injection of dexamethasone, a synthetic glucocorticoid, induces a significant reduction of REM sleep in rats [51]. In elderly men, cortisol administration determined an increase in NREM sleep and a decrease in REM sleep [52], as well as in young subjects [53]. Since CRH and cortisol exert opposite effects on NREM sleep, it is unlikely that these effects are associated to increased cortisol. More likely, these changes are a consequence of the negative feedback of cortisol on CRH release. Several studies showed that all the HPA axis mediators suppressed REM sleep indicating that this behavioral alteration is likely consequent to the cortisol increased produced by axis activation. [54].

To summarize, acute administration of cortisol promotes NREM sleep, probably via feedback inhibition of CRH. Cortisol suppresses REM sleep in humans but not in rodents.

The effects of cortisol on wakefulness are still incompletely understood, probably due to the differences in the experimental conditions of the studies performed so far. Finally, it must be kept in mind that the effects exerted by the HPA axis mediators strictly depend on their concentration on the differential interactions with receptor subtypes in the different brain areas.

Methods

To disentangle the relationship between sleep, resilience, and stress, in March 2023, we conducted a search in PUBMED https://pubmed.ncbi.nlm.nih.gov/ using the keywords "sleep resilience stress." The search produced 622 results, most of which focused either on the effects of disturbed sleep on stress resilience or on the effects of stress resilience on sleep. Of these, 382 (339 experimental studies and 43 reviews) have been published in the last 3 years (and only 5 before the year 2000) highlighting the growing interest in this research field. On the base of this search, we conducted a narrative review first to consolidate the knowledge on the positive effects of stress resilience on sleep quality and then, to explore the opposite causal link (the most representative studies are listed in Table 1).

Discussion

Resilience Improves Sleep Quality

The American Psychological Association defines resilience as "the process of adapting well in the face of adversity, trauma, tragedy, threats, or even significant sources of threat" [25]. Resilience is, thus, a protective factor against mental problems and as a dynamic process of adaptation to changes in life circumstances [55, 56].

Enhancement of resilience leads to an improvement in sleep (Table 1). Indeed, people with lower resilience are likely to develop depression associated with sleep reactivity and sleep disturbance [57]. Using self-administered questionnaires, demographic characteristics, sleep disturbance, sleep reactivity, resilience, and depressive symptoms were investigated in 584 Japanese adult volunteers. Sleep disturbance and sleep reactivity were positively associated with depressive symptoms, whereas resilience was negatively associated with depressive symptoms. The authors concluded that aggravating effects of sleep disturbance and sleep reactivity on depressive symptoms can be buffered by the improvement of resilience and, on the other hand, the negative effect of low resilience on depressive symptoms might be mitigated improving sleep quality [57] (Fig. 2). A prospective study on 1299 adolescents reported that daytime

Table 1 Most representative studies exploring the bidirectional relationship between sleep quality and resilience

| Study (first author and species)	Resilience → sleep quality	Sleep quality → resilience
Terao et al. (2022), humans	The improvement of resilience buffers the effects of disturbed sleep on depression.	Good sleep mitigates the negative effects of low resilience on depression.
Wang et al. (2020), humans	Higher resilience scores predicted better sleep quality and shorter sleep latency.	Sleep disturbance and daytime dysfunction have stronger negative effects on resilience.
Notario-Pacheco B. et al. (2011), humans	/	Worse sleep quality in subjects of low levels of resilience.
Wong et al. (2018), humans	/	Absence of sleep problems in early life determines higher behavioral control in adolescence and resilience in adulthood.
Chang et al. (2019), humans	Different levels of resilience correlate with sleep quality.	/
Liu et al. (2016), humans	Resilience as a protective factor for sleep derangements.	/
Palagini et al. (2018), humans	Low resilience may contribute to insomnia perpetuation and predisposition.	Disturbed sleep habits cause low resilience levels.
Zhou et al. (2021), humans	Resilience mitigates the aggravating effects of disturbed sleep on depression.	/
Arora et al. (2022), humans	/	Good sleep habits preserve the body health and prepare to be more resilient to stressors.
Cheng et al. (2021) and Cheng et al. (2022), humans	/	Digital cognitive behavioral therapy improves stress resilience protecting against insomnia and depression.
Bush et al. (2022), mice	/	Increased sleep amount corresponds to increased resilience.
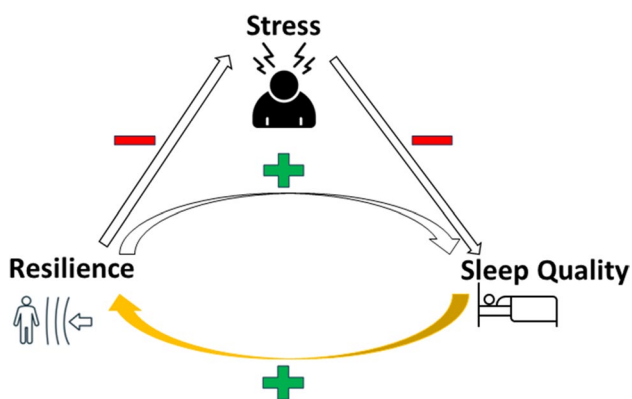
Fig. 2 Sleep, stress, and resilience. Schematic representation of the relationships between sleep, stress, and resilience. "+" and "−" indicate, respectively, positive and negative effects of these protagonists over each other. The orange arrow highlights the emerging positive correlation between sleep quality and resilience underlining the therapeutic impact of good sleep on stress resilience

dysfunction and sleep disturbance were bidirectionally associated with resilience. Higher resilience scores predicted overall better sleep quality and shorter sleep latency, but not vice versa. These findings highlight the importance of school interventions for a good sleep hygiene to improve students' resilience [58]. This bidirectional relationship may be explained by sleep and resilience influencing individuals'

brains by similar mechanisms [59]. Sleep and psychological resilience share similar neuronal networks and crucial brain hubs. An individual's ability to adapt, especially in response to potent stressors, is associated with modulating activity of the ventromedial prefrontal cortex. Similarly, the prefrontal cortex is associated with the pathophysiological outcomes of sleep disruptions. Activity in other brain regions, such as structures and circuits related to autonomic activation (including the HPA axis and the noradrenergic, serotonergic, and dopaminergic systems) and emotional regulation (hippocampus and amygdala), has similarly been linked to both sleep and resilience [60]. Another explanation is that sleep issues may cause amygdala overactivation which, in turns, may affect the ability to withstand or recover from stressors. In addition, resilient students tend to cope better with academic stress, which may influence their sleep, although to a lesser degree. This finding was also confirmed in a cross-sectional observational study, involving 681 Spanish university students [61]. Sleep quality in both men and women was significantly worse in subjects with lower resilience scores, as tested by the Pittsburgh Sleep Quality Index; on the other hand, the score on the Mental Component Summary was also significantly lower in both men and women in the lowest resilience category [61]. A longitudinal study from childhood to adulthood (3–5 to 21–26 years) found that higher sleep rhythmicity, lower tiredness, and infrequent sleep difficulties in early life predicted higher behavioral control in

adolescence which, in turn, predicted resilience in young adulthood [62]. Resilience was also predictive of overall sleep quality in another longitudinal study on children (2 to 11 years) in Taiwan [63].

In addition, a study of community-dwelling adults suggested that subjective stress is a risk factor for sleep disturbance while resilience may play a protective role [64]. Another research [65] proposed that sleep disturbance (58 subjects with Insomnia Disorder) and low resilience are associated with high sleep reactivity related to stress. Zhou and colleagues analyzed first-year college students and found that sleep quality might mediate the association between chronotype and depressive symptoms, and resilience might buffer the exacerbating effects of chronotype and sleep quality on depressive symptoms [66]. One could hypothesize a complex interplay between trait factors that contribute to insomnia related to stress (i.e., low resilience and high stress-related sleep reactivity) and the perpetuating factors of insomnia (i.e., presleep hyperarousal and emotion dysregulation). Low resilience may predispose to insomnia through low adaptation to stress, thereby contributing to sleep reactivity and heightened physiologic and emotional responses to stressful situations. Low resilience may also contribute to insomnia perpetuation through emotional and arousal dysregulation, by especially negatively merging with emotion regulation and consequently with presleep arousal [65]. High levels of resilience could significantly enhance the quality of sleep in special older population — disabled elders in China [67], and reduce the levels of perceived stress by improving psychological resilience. Several surveys supported these findings [68–70]. Using a big sample of college students ($n = 1065$), Li and his colleagues indicated the direct effect of resilience on sleep quality [69]. The negative predicted function of perceived stress on sleep quality has also been checked and confirmed among elderly population [64].

There is growing evidence that sleep and resilience are interconnected. First, those who report greater psychological resilience also exhibit more robust sleep (e.g., greater sleep efficiency, fewer and shorter awakenings after sleep onset, less light sleep, and more deep sleep) [71–73]. Similarly, those with poor sleep also report less resilience. Not only do good sleepers report greater resilience than those with insomnia, high levels of resilience also protected individuals against the effects of stress on sleep quality [65].

In a sample of Australian children and adolescents (aged 7 to 18 years) it was found that resilience and sleep problems were negatively and strongly correlated [74]; in addition, 116 dance students obtaining lower resilience scores reported poor sleep quality [75]. In a cross-sectional study including 190 patients, lower levels of resilience were associated with more sleep disturbances, while higher levels of resilience were associated with fewer sleep disturbances within age and gender diverse participant sample [76].

Individuals with high resilience possess positive characteristics (e.g., high cope self-efficacy, positive emotions, realistic optimism, and cognitive flexibility) that can help them to positively adapt and maintain good sleep quality in the face of acute or chronic stress [25]. Additionally, the existent literature has linked sleep quality with psychological resilience from a neurobiological perspective [60, 77, 78]. One possible explanation is that high resilience could maintain the HPA axis at an optimal level of activation, that is, high enough to respond to danger but not so high as to stimulate excessive fear, anxiety, and depression, thereby helping the resilient individual to avoid psychosomatic disorders such as sleep disturbance [79].

Good Sleep Stronger Stress Resilience

Historically, the relationship between sleep and stress resilience has been investigated focusing on the negative effects of the former over the latter. In particular, studies in this field highlighted the link between poor sleep (such as insomnia) and impaired stress resilience often leading to psychological distress (Table 1) [80, 81]. On the hand, there is a dearth of research investigating the positive relationship between good sleep, stronger stress resilience, and positive psychosocial resources. Since sleep is a modifiable behavior, this knowledge gap should be filled to start considering sleep hygiene as innovative tool to prevent/cure psychological impairments linked to altered stress response (Fig. 2).

A recent meta-analysis [82] on 63 articles demonstrated a clear positive relationship between sleep (quality and quantity) and psychological resilience. It must be noted, however, that this research included pooled correlational estimates which prevent defining a causal temporal link between factors. Despite this important limitation, authors speculated that, according to their research, individuals exhibiting enough good sleep were more protected to the development of chronic diseases, had better hormone regulation, and were also better cognitively equipped to cope with stressors. In other words, having good sleep habits preserves the body healthy and prepares to be more resilient to stressors by adopting adaptive coping strategies [82]. In line with the main message of this meta-analysis, it is possible to speculate that medical interventions to restore or improve sleep quality might be beneficial also in terms of stress resilience.

Indeed, a couple of studies by Cheng et al. [83•, 84•] performed during and after the COVID-19 pandemic strongly support this theory. Stressful events, such as the abovementioned pandemic, strongly contribute to sleep derangements, psychosocial functioning, and illness. The study by Cheng et al. (2021) evaluated the protective effects of prior digital cognitive-behavioral therapy for insomnia (dCBT-I) on stress resilience during the COVID-19 pandemic. More specifically, relative to a sleep education intervention, adults

who completed dCBT-I before pandemic began had lower symptoms of insomnia, lower general stress, lower depressive symptom severity, and better global health [84•]. The follow-up of these populations 1 year later fully confirmed these findings. Moreover, those who received dCBT-I by improving stress resilience were more protected compared to controls against insomnia or depression development due to reduced risk factors associated with these conditions [83•].

Basic animal research studies importantly contributed to the knowledge of the relationship between sleep and stress [2, 21, 85]. Even in this very new contest, animal research is likely to greatly accelerate our comprehension on the possibility of improving stress resilience manipulating sleep habits. Recently, Bush et al. [86•] demonstrated that keeping mice awake decreased their resilience, thus exposing them to the negative effects of stress. Conversely, increasing sleep, by selective (chemogenetic) activation of the preoptic area (responsible for initiating sleep), increased mice resilience to social stress. The authors concluded that susceptible and resilient mice, due to different sleep regulatory systems, differentially faced the intense waking experience of social stress with resilient animals that successfully recovered sleep and susceptible animals stacked in a stress-vulnerable, perpetually sleep-deprived state [86•].

Conclusions and Future Directions

In the present work, we first summarized the knowledge on the neuro-endocrine stress response (Fig. 1), the different classes of stress which we might face during lifetime, the individual predisposition to stress resilience, and susceptibility and, then, we moved to explore the role of sleep in this picture (Fig. 2). Sleep and stress resilience have a bidirectional direct correlation. The modulation of the former over the latter has been widely investigated: the higher stress resilience the better sleep quality and, on the other hand, the lower stress resilience the worse sleep quality. Many other studies have been addressed to unravel the link between disturbed sleep and low stress resilience while a completely new field of investigation concerns the positive relationship between good sleep, stronger stress resilience, and positive psychosocial resources. Sleep is a modifiable behavior, and for this reason, it is a perfect candidate as the key to start a virtuous cycle: by improving sleep it is possible to increase resilience and, in turn, to reduce stress. Finally, reducing stress allows for further sleep improvement and so on. According to this theory, it becomes crucial to better investigate the relationship between good sleep and better stress resilience, particularly focusing on the proactive interventions capable of making sleep better. In this

context, dCBT-I represents, now, the best option but many other studies are welcoming to confirm the positive effects of this intervention or to find alternative psychological/pharmacological approaches.

Many studies strongly suggest that the early-life exposure to physical and psychological stressing factors might have a key role in the development of long-term sleep disturbances both in newborns and adults, probably through epigenetic mechanisms [21]. Recently, it has been highlighted that these stressing factors would lead to permanent changes in the biological regulation of stress system, also impairing resilience [80]. It has also been shown that early-life stress exposure leads to long-term sex-dependent changes [87] at least in the hippocampus (a key structure for the HPA axis activity control). These differences may be linked to the characteristics of the placenta, which is a sexually dimorphic organ that responds differently to prenatal stress depending on the sex of the developing offspring [88]. However, specific sex-related differences in the effects of stress on sleep and resilience have not yet been studied and will need to be investigated by future studies.

Considering that disturbed sleep is a powerful stressing factor, prenatal maternal insomnia might negatively affect the physiological development of stress resilience and wake-sleep cycle in newborns with important sex-dependent repercussions even in adulthood. Further studies are needed to confirm this hypothesis which would open a completely new research field aiming at improving mothers' sleep quality during pregnancy and, through that, to enhance babies' stress resilience throughout their lifetime.

Declarations

Conflict of Interest The authors declare no competing interests.

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