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1 **STRESS & SLEEP: A RELATIONSHIP LASTING A LIFETIME**

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ABSTRACT

Stress is an adaptative response aimed at restoring body homeostasis. The classical neuroendocrine stress response involving the activation of the hypothalamic-pituitary-adrenal (HPA) axis modulates many physiological aspects, such as the wake-sleep cycle. In the present review, we will first report a series of human and rodent studies showing that each actor of the HPA axis has the potential to interfere with sleep homeostasis and, then, we will highlight how acute or chronic stress differently modulates the wake-sleep cycle. Moreover, we will present new and interesting studies dealing with the relationship between sleep and stress on a different (longer) time scale. Particularly, we will discuss how the exposure to perinatal stress, probably through epigenetic modulations, is sufficient to cause persistent sleep derangements during adult life. In light of this evidence, the main message of the present review is that the complex relationship between sleep and stress changes dramatically on the basis of the time scale considered and, consequently, “time” should be considered as a critical factor when facing this topic.

KEYWORDS

Stress, Sleep, Chronic, Acute, Epigenetics, Cortisol, Hippocampus, HPA, insomnia.

Declarations of interest: none

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1. INTRODUCTION

It has been well established that stress and sleep are intimately connected. This bidirectional relationship plays an important role among the mechanisms that allow the maintenance of body homeostasis in response to internal or external challenges (McEwen and Karatsoreos, 2015). Several animal and human studies have demonstrated that stress-inducing factors may significantly impact on the wake-sleep cycle in a variety of ways, mainly depending on type of stressors and duration of exposition (acute or chronic), as well as on interindividual differences (Koolhaas et al., 1997; Meerlo et al., 2002; Sanford et al., 2015; Kim and Dimsdale, 2007; Germain et al., 2003). On the other hand, it is well known that sleep disorders can deeply impact on several biological pathways, stress responses and, eventually, on quality of life. Even few days of sleep deprivation or circadian misalignment are enough to increase appetite, caloric intake, pro-inflammatory cytokines, blood pressure, insulin and blood glucose. Moreover, sleep deprivation alters the physiological neuroendocrine stress response by increasing the sympathetic tone and cortisol levels (McEwen and Karatsoreos, 2015). Chronic circadian disruption and reduced sleep time can even make this scenario worse, significantly increasing the risk of developing cardiovascular and metabolic disorders (diabetes and obesity) (Tobaldini et al., 2017).

Stress responses are also critically linked to temporal dynamics. This notion was already proposed several years ago to indicate that a relatively brief (acute) exposure to a stressor may increase later vulnerability to stress pathology in animals (Koolhaas et al., 1997). In recent years, a growing number of evidences highlights a new aspect of stress temporal dynamics, relevant in mediating the effects of the interaction with sleep: the moment of life in which stress is acting. In particular, it has been shown that stress exposure during the early stages of life can have an effect on adult sleep (Palagini et al., 2015). Therefore, in this manuscript, in which we aim to review the connection between stress and sleep, "time" will be emphasized as the central element of the equation. First, the mechanisms of response to stress will be examined, focusing on the epigenetic mechanisms that can mediate the long-term effects of stress acting in the early stages of life. Subsequently, we will describe the effects of acute and chronic stress on sleep, and the long-term effects of perinatal stress on adult sleep. Finally, the theoretical bases of a possible new therapeutic approach to adult sleep disorders based on the pharmacological manipulation of epigenetic mechanisms activated by perinatal stress will be discussed.

2. MECHANISMS OF THE STRESS RESPONSE

98 First, we will discuss some of the mechanisms by which stress may impact on the wake-sleep cycle.
99 Stress is an adaptative response with the purpose of restoring body homeostasis and facing ambient
100 challenges. To this aim, it modulates many different physiological functions, with different
101 interactions occurring at multiple levels, from the molecular (gene transcription regulation) to the
102 more integrated (brain activity and behavior) levels. The regulation of the wake-sleep cycle involves
103 a widely distributed neural network, multiple neurotransmitter systems, excitatory and inhibitory
104 amino acids, peptides, purines, and neuronal and non-neuronal humoral modulators. Many of the
105 same circuits, neurotransmitters, and neuromodulators are also influenced by and/or mediate the
106 effects of stress and are likely to be involved in the effects of stress on sleep (Sanford et al., 2015).

107 2.1. Stress activates the hypothalamic-pituitary-adrenal axis

108 In this review, we will mainly focus on the activation of the classical neuroendocrine stress response.
109 Essential to this response are neurons in the paraventricular nucleus of the hypothalamus, which
110 express corticotropin-releasing hormone (CRH), vasopressin (VP), and other neuropeptides driving
111 the activity of the sympatho-adrenomedullary and the hypothalamic-pituitary-adrenal (HPA) systems.
112 These two systems exert control over each other's activity, with the HPA system being slower and
113 more persistent in its actions involving hormones secreted by the adrenals (cortisol in humans or
114 corticosterone in rodents) (De Kloet et al., 1998). CRH and VP secretion leads to pituitary release of
115 adrenocorticotropin (ACTH) and adrenal gland activation, with release of glucocorticoids. HPA axis
116 activity exhibits a clearly established circadian rhythmicity that roughly parallels the activity cycle.
117 Plasma corticosteroid levels are typically highest before wakening (i.e., cortisol awakening response)
118 and lowest before sleep, corresponding in humans to early morning and late evening, respectively
119 (the reverse in rodents, which are nocturnally active). HPA axis activity also increases in response to
120 stress. While short periods of controllable stress may be beneficial to emotion and health, a lack of
121 control and uncertainty can produce a chronic state of distress, which is believed to enhance
122 vulnerability to disease. Both the stress-induced activation and the circadian rhythmicity of the HPA
123 axis are inhibited by glucocorticoid negative feedback (Jacobson and Sapolsky, 1991). This control
124 is exerted both at the hypothalamic and pituitary level where glucocorticoids inhibit the release of
125 CRH and ACTH, respectively (Figure 1).

126 Corticosteroids exert their actions by binding intracellular receptors and, consequently, modulating
127 gene expression. These receptors are part of a multiprotein complex consisting of one receptor
128 molecule and several heat shock proteins. Molecular and biochemical studies have shown the
129 existence of 2 receptor subtypes with different affinity for aldosterone and cortisol (or corticosterone),
130 respectively known as mineralcorticoid (MR) and glucocorticoid receptor (GR). GRs are expressed

131 everywhere in the brain, but they are particularly abundant in the hypothalamic CRH neurons and
132 pituitary corticotropes. Historically, MRs have rarely been related to the stress response, since the
133 control of the sodium balance through actions in the kidney and hypothalamus was considered their
134 unique homeostatic function (De Kloet et al., 1998). However, the highest expression of MRs in the
135 brain takes place outside the hypothalamus, specifically in the hippocampus, a structure that is mainly
136 involved in learning and memory processes. Interestingly, MR selectivity for aldosterone is lost in
137 the hippocampus, thus, in this structure, cortisol (or corticosterone) activates 2 different pathways via
138 MRs and GRs (Reul and de Kloet, 1985). Another peculiar and often underestimated feature of the
139 hippocampus is that this structure plays a key role in the regulation of HPA axis activity (Figure 1).
140 In particular, the hippocampus exerts an inhibitory effect on hypothalamic CRH release (Jacobson
141 and Sapolsky, 1991), thus participating in the restraint (negative feedback) of the stress response and
142 in the dampening of HPA rhythmicity (primarily by raising the nadir corticosteroid level toward that
143 of the peak). So, the hippocampus can be considered a functional component of the HPA axis. In the
144 hippocampus, corticosterone binds to MRs with a 10-fold higher affinity than to GRs (Veldhuis et
145 al., 1982). The MRs are substantially occupied even at basal levels of HPA axis activity, suggesting
146 that these receptors are implicated in the maintenance of basal activity of the stress system. High
147 concentrations of corticosteroids progressively saturate GRs, implying that the suppression of stress
148 induced HPA activity occurs, in particular, through GRs (De Kloet et al., 1998).

149

150 2.1.1. Early-life stress and long-term HPA axis alterations

151 Glucocorticoids are essential for life, influencing virtually every tissue and affecting a wide range of
152 physiological functions such as metabolism, blood pressure, breathing, immune system, and behavior.
153 Both acute and chronic stress condition may alter the response of the HPA axis (including the negative
154 feedback loop exerted by the hippocampus), entailing increased levels of circulating corticosteroids
155 which predispose the body to cope in an emergency. However, the period of life when the stress is
156 faced can exert a specific impact on the duration and intensity of HPA axis activation. There is now
157 convincing evidence that early life experience can cause changes in the stress response system that
158 persist into adulthood. Indeed, it has been proposed (Reynolds, 2013) that some factors acting during
159 critical windows of development may lead to permanent changes in the fetus which initially promote
160 survival, but then predispose the individual to later life disease. The term “factors” includes a batch
161 of different conditions such as alteration in maternal care, depression, abuse, malnutrition (either pre-
162 or post-natal), and traumatic events; these have been identified by an increasing number of studies
163 performed in recent years (Lucassen et al., 2013). It is important to note, however, that not all the
164 early-life events necessary negatively impacts on adult phenotype. For instance, several studies

(Lehmann et al., 2000) suggest that neonatal handling and/or maternal separation may have almost opposite effects depending on their duration (i.e., 5-15 min per day versus several hours per day). These events can differently impact on the HPA axis either increasing or decreasing its activity. Whether or not such HPA axis modulations will have good or bad outcomes during adulthood depends on the nature of the factor (quality and quantity) as well as the nature of the individual (genes and gender) and the interaction with the environment. However, for the purposes of the present review, we will focus on the negative correlation between early-life events and adult phenotypes.

Different aspects of maternal behavior (feeding, passive contact or non-nutritive sucking, licking and grooming) might affect HPA axis regulation in newborns. It is likely that these maternal behaviors act in concert to limit and prevent stress hormones from exceeding their optimal level (Levine, 2001). It has been shown that disruption in the mother–infant relationship is enough to exert several negative consequences. Indeed, lack of maternal behavior impacts on hippocampal neurogenesis (Meaney, 2001; Oomen et al., 2009) and neuronal plasticity increasing vulnerability to aging and psychopathology (Cirulli et al., 2003). Naturally occurring variations in maternal care alter the expression of genes involved in behavioral and endocrine responses to stress (Meaney, 2001; Plotsky et al., 2005); moreover, it negatively impacts on energy metabolism (Pankevich et al., 2009) and the cardiovascular system in adults (Matthews et al., 2011). Interestingly, some of these studies also highlighted gender-dependent outcomes. For instance, cross-fostering produced increased abdominal adiposity and increased values of systolic blood pressure only in adult male but not in female mice (Matthews et al., 2011). Likewise, hippocampal neurogenesis has been found to increase in male and to decrease in female mice after maternal deprivation (Oomen et al., 2009).

Besides maternal behavior, it is widely accepted that maternal diet and adiposity have an impact on the offspring's development. There is a clearly established relationship between maternal obesity and offspring obesity and the children of obese mothers are more likely to develop metabolic complications such as diabetes later in life (Pankevich et al., 2009). On the other hand, severe prenatal malnutrition is proved to affect HPA axis activity and feeding circuitry, resulting in adult obesity and comorbidities (Spencer, 2013). Similarly, the incidence of psychiatric disorders and cognitive impairment is highly increased in subjects who experienced, during their childhood, maternal depression, sexual abuse, or catastrophic events (Lucassen et al., 2013). Finally, early life stress, induced by behavioral stressors or adverse childhood experiences, is highly correlated with ischemic heart disease in adulthood, more so than the traditional risk factors (Loria et al., 2014).

Numerous studies have tried to understand how early-life stress can impact on adult life. The hippocampus, among the other brain regions, seems the most fitting candidate to be permanently modulated by stress conditions. Indeed, the hippocampus is particularly sensitive to the early-life

environment because it has a high degree of structural and synaptic plasticity, it undergoes dynamic changes in neuronal connectivity (Lucassen et al., 2013), and it is rich in stress-hormone receptors (GRs and MRs). This high receptor concentration makes the hippocampus a key structure in the regulation of the physiological stress response. Indeed, the activation of the hippocampus through these receptors has the ultimate effect to inhibit the release of CRH from the hypothalamus (Jacobson and Sapolsky, 1991). Finally, the human hippocampus develops between the last trimester of gestation and 16 years of age (Arnold and Trojanowski, 1996); in rodents this occurs between embryonic day 18 and postnatal weeks 2–3 (Altman and Bayer, 1990). Therefore, in offspring hippocampus modulation may occur both in utero and during the post-natal period, invariably entailing HPA axis derangements that can be responsible for adult predisposition to numerous diseases (Figure 1). Levels of cortisol in pregnant women naturally increase during the last trimester of gestation (Reynolds, 2013). However, even if lipophilic steroids easily cross the placenta, fetal glucocorticoid levels are much lower than maternal levels (Seckl, 2004). In fact, the 11 β -hydroxysteroid dehydrogenase type 2 (11 β -HSD2), which catalyzes the rapid conversion of active physiological glucocorticoids (cortisol and corticosterone) to inert 11-keto forms (cortisone and 11-dehydrocorticosterone), is highly expressed in the placenta. Nevertheless, conditions of stress during pregnancy can increase maternal cortisol level beyond the limit of action of 11 β -HSD2, thus overexposing the fetus to glucocorticoids. The large amount of steroids in the fetus, probably through epigenetic modifications (cf. paragraph 2.1.2), downregulates hippocampal GR expression eventually reducing the inhibiting role that this structure exercises on the HPA axis activity (i.e. hyperactivating the HPA axis) (Pankevich et al., 2009; Seckl, 2004). Similarly, the lack of maternal care and sensory stimulation (van Oers et al., 1999) as well as under or over nutrition (Laus et al., 2011; Schmidt et al., 2006) in the early postnatal period is sufficient to increase cortisol levels in newborns, possibly affecting the HPA axis development (Figure 1).

2.1.2. Role of epigenetic mechanisms in long-term effects of early-life stress

The stress-related cortisol increase in fetuses or newborns impacts on HPA development possibly through epigenetic modulation of CRH, GR, and MR expression, particularly in the hippocampus (please refer to Table 1 for more detail on epigenetic inheritance systems). Different studies performed in rats highlighted the relevance of GR exon I₇ (in the gene promoter region) for later life consequences and its potential as a target for reversal of early-life effects (Weaver et al., 2004; Weaver et al., 2005). In particular, the investigators showed that poor maternal care was responsible for the hypermethylation of GR promoter and the consequent decrease in the number of hippocampal GRs in the offspring (Weaver et al., 2004). Since the hippocampus plays a key role in the negative

233 feedback regulation of the HPA axis, a low number of GRs in this area reduces hippocampal
234 inhibition of the HPA axis. Consequently, poor maternal care reduces hippocampal GRs in the
235 offspring, eventually leading to exacerbated HPA axis activity and increased corticosteroid levels in
236 adults. Rescue experiments showed that in perinatally stressed adult rats the increased corticosterone
237 levels normalize after demethylation of the hippocampal GR promoter (Weaver et al., 2004; Weaver
238 et al., 2005), further suggesting epigenetic involvement in HPA axis alterations. Epigenetic
239 modifications resulting from perinatal stress conditions also included demethylation of hypothalamic
240 CRH and VP promoter (Chen et al., 2012; Murgatroyd et al., 2009) and consequently, increased CRH
241 and VP levels in adults.

242

243 3. EFFECTS OF STRESS ON SLEEP

244 Stressful conditions entail a plethora of body responses involving molecular, hormonal,
245 neurochemical, and behavioral changes aimed at coping with external challenges and maintaining
246 internal homeostasis. Stress response largely varies according to the characteristics of the stressor
247 applied (e.g., duration, intensity, controllability, and predictability) and of the subject experiencing
248 stress (e.g., individual stress coping strategies, relative resilience, and vulnerability) (Sanford et al.,
249 2015). Modulation of the HPA axis activity plays a central role in these processes, and the various
250 actors of this axis can exert a deep impact on sleep function. This may have important consequences
251 on the health of subjects. In fact, it is a shared experience that a good night's sleep improves physical
252 and cognitive performance, while lack of sleep worsens our performance in daily activities. This
253 subjective experience is supported by scientific evidence (review in Goel et al., 2013): human subjects
254 with reduced sleep duration (less than 6 hours / night) (Gildner et al., 2014) or with disturbed sleep,
255 as patients with sleep apnea (Yaffe et al., 2011), have a significant reduction in memory performance
256 and cognitive assessment. Studies on animal models (Karatsoreos et al., 2011; Kwon et al., 2015)
257 also led to similar conclusions. Emerging evidence suggests that sleep deprivation and circadian
258 rhythm disruption may increase the risk for the development of Alzheimer's disease and other
259 neurodegenerative brain pathologies, mainly by interfering with the glymphatic-vascular-lymphatic
260 clearance of brain macromolecules and by increasing oxidative stress (Wu et al., 2019). Finally, sleep
261 deprivation itself can represent a stress, enhancer of other stressors that have negative consequences
262 for the brain and many body systems (McEwen & Karatsoreos, 2015). A growing body of evidences
263 correlates a reduction of duration and/or quality of sleep with alterations in endocrine and metabolic
264 function, favoring the development of obesity and type 2 diabetes (Van Cauter & Tasali, 2013). Sleep
265 deprivation can decrease parasympathetic tone, increase corticosteroids and metabolic hormones
266 when they should be low (flattening of rhythms), and increase level of proinflammatory cytokines

(Spiegel et al., 2004; Vgontzas et al., 2004). However, since the outcome of this approach is to evaluate the sleep phenotype after application of stressors, sleep deprivation or sleep derangements are not included in the list of stress-inducing factors in order to prevent circular discussion. Therefore, in this section we will discuss first the mechanisms through which the activation of the HPA axis produced by stress can modify sleep and, then, the specific effects on sleep exerted by acute or chronic stress, or a stress applied in the early stages of life.

3.1. Effects of HPA stress mediators on sleep

There are significant overlaps between neural networks and neurochemistry underlying the stress response and that regulating arousal and sleep. In fact, the regulation of the wake-sleep cycle involves multiple neurotransmitters and neuromodulators, most of which plays also a role in the stress response. In the following paragraphs, we will discuss the effect exerted by the stress mediators of the HPA axis on the wake-sleep cycle either directly or indirectly through the modulation of circadian rhythms. Even if it is generally accepted that the products of the HPA axis exert a sleep-reducing effect by stimulating waking, experimental evidence shows that the mechanisms of action of the different mediators and the timing of their effects are quite different.

3.1.1. CRH

CRH receptors are densely distributed in the basal prosencephalic areas, thalamus, hypothalamus, mesencephalus, brainstem, and pons (De Souza, 1987). All these areas are involved in cerebral activation and waking maintenance, thus suggesting an involvement of CRH in wakefulness regulation. There are three related CRH receptor subtypes, CRH-R1, CRH-R2 α , and CRH-R2 β , that differ from each other in anatomical distribution as well as in pharmacological profile. CRH-R1 is widespread in the brain and is also found in the anterior and intermediate lobes of the pituitary gland, whereas CRH-R2 is confined to subcortical structures in the brain, and is either undetectable or only detected in scattered cells in the pituitary gland (Chang and Opp, 1999). A series of studies documented that intracerebroventricular (ICV) administration of CRH in rats produced many of the signs associated with anxiety in humans, including increased wakefulness (Chang and Opp, 1998) and, symmetrically, decreased non-rapid-eye-movement (NREM) and rapid-eye-movement (REM) sleep (Romanowski et al., 2010) (Table 2), altered locomotor activity, and an exaggerated startle response (Swerdlow et al., 1986). The major impact of CRH on wakefulness and NREM sleep regulation seemed to be exerted by central CRH-R1 (Romanowski et al., 2010). However, studies using non-selective CRH receptor antagonists such as α -helical ovine CRH₉₋₄₁ (α h-CRH) and astressin reported conflicting results. In one study the ICV administration of either α h-CRH or

301 astressin to rats at dark onset reduced the amount of time spent awake immediately after the injection
302 or with a longer delay, respectively (Chang and Opp, 1999). Interestingly, when these compounds
303 were administered at the beginning of the light period (resting phase in rodents), they failed to affect
304 wakefulness, which supports the view that CRH contributes to the regulation of physiological waking
305 periods. Similarly, CRH antisense oligodeoxynucleotides reduced spontaneous wakefulness during
306 the dark period, but not during the light period (Chang and Opp, 2004). On the contrary, another study
307 found that α h-CRH injections at dark onset exerted no effect on spontaneous sleep-wake behavior
308 (Gonzalez and Valatx, 1997), whereas REM sleep induced by immobilization stress appeared to be
309 abolished and the rebound of REM sleep after sleep-deprivation was reduced (Gonzalez and Valatx,
310 1997). Accordingly, mice with overexpression of CRH showed an increased basal level of REM sleep
311 compared to controls and enhanced recovery REM sleep after 6h sleep deprivation (Kimura et al.,
312 2010).

313 In a study in humans, the pulsatile intravenous administration of CRH prompted a decrease in stage
314 N3 of NREM sleep, an increase in intermittent wakefulness and an increase in the time spent in REM
315 sleep during the first third of the night (Steiger et al., 2013). On the contrary, 4 weeks of infusion of
316 the CRH-R1 antagonist R121919 increased the amount of NREM sleep, while decreasing the number
317 of awakenings and REM density (Held et al., 2004).

318 In conclusion, while it is well consolidated that CRH promotes wakefulness and, consequently,
319 reduces NREM sleep both in humans and rodents (Table 2), its action on REM sleep has not been
320 totally clarify yet and, most likely, it diverges between species (Table 2).

321

322 3.1.2. ACTH

323 In a rat study, the ICV injection of ACTH promoted wakefulness, whereas injections of its
324 derivatives, desacetyl-alpha-melanocyte stimulating hormone and corticotropin-like intermediate
325 lobe peptide, increased NREM sleep and REM sleep, respectively (Chastrette et al., 1990). In young
326 male volunteers, sleep electroencephalographic (EEG) activity changes occurred after pulsatile
327 intravenous administration of ebitatide, an ACTH analog. Specifically, in these subjects NREM sleep
328 decreased whereas sleep latency and wakefulness increased during the first third of the night (Steiger
329 et al., 1991). In intact cats, ACTH infusions suppressed REM sleep (Koranyi et al., 1971) and, in rats,
330 it significantly increased sleep latency and wake time while decreasing NREM sleep time (Tsutsui et
331 al., 2015). Since sleep disturbances in depressive patients are characterized by an increase in sleep
332 latency and a decrease in NREM sleep time (Holshoe, 2009), it has been proposed that chronic
333 administration of ACTH in rats might represent a valid animal model for human depression (Tsutsui
334 et al., 2015) (Table 2).

335 Similar to CRH, available evidence from humans and animals indicates that ACTH stimulates
336 wakefulness at the expenses of NREM sleep (Table 2). Even in this case, the picture concerning the
337 effects of ACTH on REM sleep is still incomplete.

338

339 3.1.3. Cortisol (and corticosterone)

340 Large doses of corticosterone in adrenalectomized rats decreased the amount of NREM sleep
341 (Bradbury et al., 1998). On the other hand, lower doses of corticosterone in intact rats seemed to have
342 a biphasic effect (Table 2), first increasing and then decreasing wakefulness. The initial alerting effect
343 of corticosterone was also accompanied by a slight decrease in NREM sleep while REM sleep was
344 not affected (Vazquez-Palacios et al., 2001).

345 In young men, it has been reported that cortisol administration reduced REM sleep and slightly
346 increased NREM sleep (Born et al., 1991). Accordingly, REM sleep decreased and NREM sleep
347 increased in a similar study performed in elderly men (Bohlhalter et al., 1997). Since CRH and
348 cortisol seem to exert opposite effects on NREM sleep, at least in humans, it is reasonable to suppose
349 that these effects do not depend on cortisol itself but are mainly due to the negative feedback
350 inhibition exerted by cortisol on endogenous CRH production. On the other hand, because CRH,
351 ACTH, and cortisol diminish REM sleep, this effect seems to be mediated by cortisol itself after the
352 administration of each of these hormones (Steiger, 2007) (Table 2).

353 Altogether, while it is well known that HPA axis perturbations affect the wake-sleep cycle, the exact
354 role exerted by cortisol (and corticosterone) in this context is still controversial (Table 2). Indeed,
355 rodent and human studies failed to provide a conclusive picture of the effects of cortisol
356 (corticosterone) on wakefulness or REM sleep while they even showed contrasting consequences on
357 NREM sleep.

358 Finally, it is important to highlight that at least some of the contrasting findings shown in Table 2
359 might be due to experimental conditions rather than the real actions of stress mediators. Indeed, most
360 of the above-mentioned studies have been performed via exogenous administration of
361 CRH/ACTH/cortisol or their analogous/antagonists. Under real physiological conditions, however, it
362 is likely that the actions of stress modulators on the wake-sleep cycle is highly dependent not only on
363 the amount of each circulating molecule but also on how they differentially interact with their receptor
364 subtypes in different brain structures.

365

366

367 3.1.4. Possible effects of glucocorticoids on sleep through the modulation of circadian clocks

368 It is important to note that besides the direct effect they exert on sleep, glucocorticoids might also
369 modulate sleep indirectly through their influence on circadian clocks. Consequently, in this paragraph
370 we will briefly introduce the circadian clock system and then we will illustrate its potential
371 modulation by glucocorticoids.

372 The 24-hour rotation of the earth strongly affects animal physiology, biology and behavior (such as
373 wake-sleep cycle rhythmicity). Evolution has equipped almost all organisms with an elaborate
374 intrinsic timing system, the so-called clock system which creates internal circadian rhythmicity, in
375 order to deal with these recurring changes. A primary role of the circadian clock is to entrain the
376 organism to environmental cues, so that an animal can anticipate fluctuations in the environment and
377 determine key issues such as food availability, predator risk, and the likelihood of reproductive
378 success. Furthermore, the circadian system is critical to the synchronization and relative phasing of
379 various internal physiological processes that are essential for the optimization of responses to
380 environmental fluctuations and for the strengthening of homeostatic control mechanisms (Kalsbeek
381 et al., 2012).

382 The hypothalamic suprachiasmatic nucleus (SCN) represents the central master clock of the circadian
383 clock system. SCN is under the strong influence of light/dark input from the eyes, whereas the
384 peripheral clocks behave as subordinates, being subjugated by the former through mechanisms which
385 remain still unclear (Charmandari et al., 2011). At the molecular level, circadian clock rhythms are
386 based on autoregulatory feedback loops involving clock genes that cycle with a period of about 24 h.
387 These genes include the Circadian Locomotor Output Cycle Kaput (CLOCK), its heterodimer partner
388 Brain Muscle-Arnt-Like protein 1 (BMAL1) and other essential negative regulators, such as the
389 Periods (PER1-3) and the nuclear hormone receptors RevErb α (Takahashi et al., 2008). Besides the
390 strong influence exerted by the SCN, peripheral clocks are also set to external time by different
391 regulatory (neural, hormonal, temperature, metabolic control) pathways. Among others, steroids can
392 directly or indirectly modulate clock gene expressions through GR binding. Since the SCN lacks GRs,
393 glucocorticoids cannot directly modulate central rhythms (Balsalobre et al., 2000). On the other hand,
394 they strongly influence peripheral rhythmicity. Unbound GRs reside in the cytoplasm, and once the
395 glucocorticoid binds to the GR, the complex travels towards the nucleus where it can bind the
396 glucocorticoid response element (GRE) in the promotor region of target genes, thereby positively (as
397 for Per1) or negatively (as for RevErb α) regulating gene expression. Alternatively, the glucocorticoid-
398 GR complex can physically interact with other transcriptional factors, altering the activities of the
399 latter on their own responsive genes (Chrousos and Kino, 2005; Gross and Cidlowski, 2008).
400 Glucocorticoids acutely induced Per1 gene expression in rodent (Balsalobre et al., 2000), canine
401 (Ohmori et al., 2013), and human (Fukuoka et al., 2005) peripheral blood mononucleate cells and

affect rhythmic Per1 (Balsalobre et al., 2000; Mongrain et al., 2010; Yamamoto et al., 2005) and Per2 (Curie et al., 2015; Segall and Amir, 2010) expression in rodent peripheral clocks. Accordingly, adrenalectomy modulated circadian clock gene mRNA abundance with a tissue-dependent effect. In mice the elimination of plasma corticosterone and its rhythmicity resulted in significant inhibition of Per1 mRNA in the visceral adipose tissue, liver, jejunum, and splenocytes but not in the kidney, as well as a decrease in the mRNA levels of some other clock genes (Sotak et al., 2016). The effect of glucocorticoids on Per1 appeared to occur directly through the GRE in the Per1 gene (Yamamoto et al., 2005), and, since transcription of clock genes is regulated via mutual feedback regulation by other clock gene products (Takahashi et al., 2008; Yamamoto et al., 2005), changes in the accumulation of the PER1 protein are likely to influence the expression of other clock genes. Similarly, in humans, the intravenous administration of hydrocortisone strongly affected Per1 and partially Per3 expression whereas it did not affect Per2 expression (Yurtsever et al., 2016). Besides entraining peripheral clocks at a molecular level, glucocorticoids seems to be also involved in the entrainment of behavioral rhythmicity such as wake-sleep cycle rhythmicity. Adrenalectomized rats showed an accelerated rate of re-entrainment to a shifted light-dark cycle (Sage et al., 2004). In adrenal-specific clock knockdown mice kept under constant darkness conditions, the amplitude of plasma corticosterone rhythm as well as their behavioral rhythm was severely dampened (Son et al., 2008). This indicated that in the absence of light as a timekeeping cue, the rhythm in corticosterone was an important factor driving locomotor activity (Kalsbeek et al., 2012). Indeed, inhibiting corticosterone production in mice resulted either in advanced or delayed behavioral resynchronization, depending on the time of injection and the direction of the phase change (Kiessling et al., 2010). Taken together, these findings indicate that, as well as entraining peripheral clocks at the molecular level, corticosterone acts as a regulator of behavioral adaptation to phase shifts, possibly through an indirect feedback to the SCN (Kalsbeek et al., 2012).

3.2. Effects of acute stress on sleep

In animal studies, a variety of protocols have been developed to investigate the consequences of acute stress on hypnic phenotype. Due to the large variety of responses reported in these studies, it is not possible to draw a unifying causal mechanism linking acute stress and hypnic derangements. Indeed, even if it is well known that acute stress invariably entails sleep loss in rodents, the following sleep rebound may vary depending on the type/duration of the applied stressor with considerable interindividual differences (possibly linked to the level of activation of the HPA axis). A **widely used** protocol to produce stress in rodents is immobilization because it does not entail physical pain and can be considered as only a psychological stress. As a rule of thumb, acute

immobilization, which is usually performed for 1 or 2 hours, produces a sleep debt in both rats and mice. Generally, this sleep debt is paid off by increasing the time spent asleep during the following hours. This sleep rebound mainly concerns REM sleep (Bouyer et al., 1998; Marinesco et al., 1999; Meerlo et al., 2001b; Pawlyk et al., 2008; Descamps and Cespuglio, 2010). Conversely, restraint stress does not appear to have a major effect on the period or phase of the activity period (Meerlo et al., 2002) indicating that this protocol probably does not affect SCN activity.

The exposure of rodents to intermittent brief *electrical shocks* represents another widely used acute stress protocol. In this case, of course, the procedure also includes pain that must be considered in subsequent analyses as a potential source of interindividual variability. However, contrary to restraint, electrical shock is usually associated with a decrease in the animals' subsequent total sleep time and, particularly, in REM sleep time (Pawlyk et al., 2008). Similarly, fear conditioning procedures entail a REM decrease during both the stimulus application (shock training) and cue exposure (Sanford et al., 2003) in different mouse strains.

Several studies have shown that *social conflicts* are one of the most potent stressors in terms of classical indicators of the stress response such as secretion of catecholamines and corticosterone. Moreover, this paradigm is probably the best way to mimic a stress-inducing condition which can be physiologically encountered in everyday life by rodents. Several studies in rats have shown that social stress may result in severely disturbed physiological and behavioral rhythms that can last for several days, up to weeks, after the conflict, particularly concerning activity patterns, body temperature, and heart rate. Regarding locomotor activity, the amplitude reduction is mainly due to a decrease in activity during the animal's activity phase. As far as body temperature is concerned, the amplitude decrease is caused by an increase in temperature during the resting phase. Also, the amplitude of the daily heart rate rhythm is reduced, but this effect may be due to both an increase during the resting phase as well as a decrease during the active phase (Meerlo et al., 2002). Despite this evidence, the social conflict does not affect the endogenous pacemaker's sensitivity to light, and the reduction of the temperature and activity amplitude do not appear to reflect a reduction in amplitude of the SCN activity (Meerlo et al., 2002).

Social defeat has also been found to have immediate effects on subsequent sleep: rats (Meerlo et al., 2001a; Meerlo et al., 1997) and mice (Meerlo and Turek, 2001) showed increased amounts of NREM sleep and/or increased NREM sleep intensity, as reflected in elevated EEG slow wave activity (SWA), and a strong reduction in REM sleep in the first couple of hours after the conflict (Kamphuis et al., 2015). The SWA increase was not explained by sleep loss per se, as it was significantly higher than in animals that had been sleep deprived through gentle stimulation for the same duration. Interestingly, the increase in NREM sleep SWA, as well as REM sleep suppression, was not different

470 between animals that had won and animals that had lost the conflict, which indicates that these
471 alterations were caused by the conflict per se and not by the outcome. Similarly, the peak response in
472 blood pressure, heart rate, and corticosterone, were similar between winners and losers, but these
473 alterations persisted longer in the losers (Kamphuis et al., 2015).

474 Altogether, social conflict may represent an intense form of wakefulness that requires more intense
475 recovery sleep. Indeed, the SWA increase after the conflict agrees with the synaptic homeostasis
476 hypothesis which states that intense wakefulness is associated with large synaptic potentiation and,
477 as a result, with a higher synchronous NREM sleep and slow waves of higher amplitude (Tononi and
478 Cirelli, 2006).

479

480 In humans, the effects of acute stress on the wake-sleep cycle have only marginally been investigated.
481 Moreover, except for Post-Traumatic Stress Disorder (PTSD) patients, only few studies were
482 performed with replicated designs on groups of participants exposed to specific types of stressors
483 (Germain et al., 2003; Kim and Dimsdale, 2007). However, one of the most recurrent finding is that
484 the exposure of healthy subjects to acute experimental psychological stress (e.g. telling them before
485 bedtime that the next morning they would have given a speech) produces REM sleep alterations more
486 frequently than NREM sleep alterations (Kim and Dimsdale, 2007; Cartwright, 1983; Pillar et al.,
487 2000; Reynolds et al., 1993). Interestingly, this finding is in line with what has been reported in
488 rodents exposed to immobilization protocol, a paradigm of psychological stress (Bouyer et al., 1998;
489 Marinesco et al., 1999; Meerlo et al., 2001b; Pawlyk et al., 2008; Descamps and Cespuglio, 2010).
490 In humans not only the nature and length of the stressor, but most importantly, the individual
491 psychophysiological reactivity and the capacity to cope with stressful situations may determine the
492 sleep outcome. It has been postulated that an attenuation of REM sleep phasic activity after
493 experimental stress exposure may reflect adaptive regulation of waking emotional arousal system of
494 the individual (Germain et al., 2003). More generally, negative emotions triggered by unfamiliar
495 environments (such as sleep laboratories) entail lower sleep efficiency (percentage of total sleep time
496 during the recording time), frequent awakenings, decreased REM and NREM sleep (Kim and
497 Dimsdale, 2007). Apart from laboratory conditions, investigators have also examined several daily
498 life stressors including acute stressful events such as bereavement (for an overview see Kim and
499 Dimsdale, 2007). Results suggest that daily life stressors may produce several changes in sleep
500 architecture including reduced REM sleep latency, increased time spent in REM sleep, and reduced
501 time spent in NREM sleep (Kim and Dimsdale, 2007). Another common category of stressors is that
502 characterized by traumatic events. Similar to acute laboratory adaptation test, life-threatening injury
503 reduces total sleep time also increasing the number of awakenings, it increases REM sleep latency

504 while reducing time spent in REM sleep and in NREM sleep (Kim and Dimsdale, 2007). These
505 comparable changes in sleep pattern might indicate that the effects of stressor exposure may have
506 similar time course (i.e., immediate effects of stress on sleep) regardless of the intensity of the
507 stressor. Traumatized patients without PTSD whose wake-sleep cycle was recorded in within 1
508 month from injury showed reduced total sleep time, increased number of awakenings, and increased
509 REM sleep density (frequency of eye movements during REM sleep) when compared to healthy
510 controls (Mellman et al., 2002). During the subsequent follow-up, patients that developed PTSD
511 showed an increased number of REM sleep episodes with a shorter average duration compared to
512 patients that did not develop PTSD (Mellman et al., 2002).

513 It is interesting to notice that one of the most diffused models of insomnia, the 3P model (based on
514 the interaction of Predisposing, Precipitating, and Perpetuating factors), has been built considering
515 the effect of acute stress on sleep (Spielman et al., 1987). According to this model, predisposed
516 individuals may develop acute/transient insomnia after a precipitating factor, such as an acute stress,
517 while perpetuating psychological and behavioral factors may contribute to the development of
518 chronic insomnia forms. Similar to rodents exposed to electrical shock or to social conflict protocols,
519 insomnia patients presents a moderate but significant reduction in REM sleep time and also a
520 reduction in NREM sleep time. These data are consistent with the hypothesis that insomnia symptoms
521 may be due to physiological cognitive and somatic hyperarousal related to the hyperactivation of the
522 stress system, including the HPA axis and inflammatory system (Riemann et al., 2015; Riemann et
523 al., 2010). Indeed, subjects with elevated stress-related sleep reactivity (degree to which the person
524 is vulnerable to sleep disturbance when exposed to stress) are more prone to develop chronic insomnia
525 (Kalmbach et al., 2018) suggesting that, in humans, dysregulation of the stress response rather than
526 general hyperarousal may be a more pertinent marker of risk to develop sleep disturbances after an
527 acute stress (Kalmbach et al., 2018).

528 Despite significant inter-study and inter-species differences, REM sleep deregulation seems the most
529 common hypnic feature affected by acute stress both in rodents and humans, particularly in PTSD
530 patients.

531

532 3.3. Effects of chronic stress on sleep

533 Chronic stress has been reported to disrupt sleep in a variety of **situations**. Several experimental
534 studies in laboratory rodents have applied different kinds of stimuli for periods up to several weeks,
535 with the effects on sleep and circadian rhythmicity then being investigated. For instance, in the same
536 study rats were exposed for 4 consecutive days either to 22 h/day of *immobilization*, *forced swimming*,
537 or *footshock* stress protocol (Papale et al., 2005). Each kind of stress promoted changes in a

538 differential fashion; during the diurnal phase, while immobilization and forced swimming led to a
539 reduction in sleep efficiency during all 4 days, immobilization was the only stressor that resulted in
540 a significant decrease in sleep efficiency and a decrease in NREM and REM sleep throughout the
541 entire period of recording. Forced swimming produced a reduction in NREM sleep and augmented
542 REM sleep only during the first day of stress exposure. Footshock produced alterations in sleep
543 efficiency and a decrease in NREM and REM sleep only on the two last days (Papale et al., 2005).
544 Footshock entailed a reduction in total sleep and REM sleep in rats only during the first day, even
545 when the protocol was protracted up to 14 days (Kant et al., 1995). This limited effect might be linked
546 to the fact that stress predictability, as well as stress controllability, can influence the perception of
547 the stressor and modulate the direction of its effects on sleep (Sanford et al., 2015).

548 Similarly, repeated exposure to a *cued fear conditioning procedure* specifically reduced REM sleep
549 in both rats (Sanford et al., 2001) and mice (Sanford et al., 2003). In the rat study (Sanford et al.,
550 2001), sleep was recorded immediately after the fear conditioning procedure. In the mouse study
551 (Sanford et al., 2003), which utilized 15 tone-shock pairings, sleep was recorded up to 24 h after
552 training, immediately after the presentation of 15 tones. These similar findings in different species
553 suggested that the reduction in REM may be a fundamental response of organisms to stress.

554 Once again, *repeated fighting and/or being defeated in a social interaction* may represent a more
555 naturally occurring stressor in social species such as rats and mice. This technique involves an
556 ethological form of stress related to territorial aggression in rodents and has numerous advantages
557 when attempting to understand the ways in which behavioral and molecular adaptations develop over
558 time in response to stressful experiences. One advantage is that key behavioral endpoints that are
559 altered by chronic social conflict (e.g., social interaction) are sensitive to chronic but not acute
560 treatment with standard antidepressants and acute treatment with ketamine, both of which resemble
561 the time courses of therapeutic drug actions in humans. In addition, chronic social conflict can reveal
562 separate “susceptible” and “resilient” populations, potentially modeling individual differences in
563 stress susceptibility in humans. Chronic social conflict effects can endure beyond the termination of
564 the stressor, making it a particularly appealing method with which to study some of the persistent
565 characteristics of stress-related psychiatric illnesses as they occur in clinical settings (Wells et al.,
566 2017). In rats, this paradigm of chronic stress entails long-lasting consequences also on daily rhythms
567 of heart rate, blood pressure and body temperature in rats that do not depend on the physical intensity
568 of the fight but largely on how the subjects deal with the conflict (Meerlo et al., 1999). In mice, it has
569 been shown that chronic social conflict profoundly impacts on the wake-sleep cycle. Particularly, it
570 increases the time spent in REM sleep and the number of REM sleep bouts; it also increases the time
571 spent in NREM sleep, and conversely it decreases the amount of time spent in wakefulness (Wells et

572 al., 2017). Some of these effects **can be reversed by the cessation** of chronic social conflict, while
573 others persisted through the recovery period, in which reductions in circadian amplitude of body
574 temperature and motor activity, and increases in time spent in NREM sleep, were present (Wells et
575 al., 2017). A brief increase in REM sleep time after 10 days of social conflict was also independently
576 reported by another experiment in which, contrary to what has been described **for** acute protocols
577 (Kamphuis et al., 2015), no change in SWA was detected (Olini et al., 2017).

578
579 **As expected, chronic stressors deeply impact also human sleep architecture as it has been reported in**
580 **cases of marital separation (Cartwright and Wood, 1991), shift works (Kim and Dimsdale, 2007),**
581 **burnout patients (Armon et al., 2008), or people who experienced lack of social support in the work**
582 **environment (Gadinger et al., 2009; Nomura et al., 2009). In particular, marital separation in non-**
583 **depressed persons resulted in the reduction of time spent in NREM sleep and the increase of the time**
584 **spent in REM sleep, accompanied by a decreased of REM sleep latency (Cartwright and Wood,**
585 **1991). Similarly, studies on shift workers reported that these subjects had longer NREM sleep latency,**
586 **decreased amount of NREM sleep, increased amount of REM sleep, and shorter REM sleep latency,**
587 **compared to students (Goncharenko, 1979). A reduction of time spent in NREM sleep was also**
588 **recorded in those subjects worried about going to work the next morning (Kecklund and Akerstedt,**
589 **2004; Soderstrom et al., 2004).**

590 **One of the dominating models in the field of psychosocial work (chronic) stress is the Job–Demand–**
591 **Control–Support (JDCS) model (Johnson et al., 1989). The central tenet of the JDCS model is an**
592 **increasing likelihood of mental and physical impairment with increasing job demands and decreasing**
593 **job control and social support. Thus, the most adverse health outcomes can be expected in**
594 **high-demand jobs with low job control and poor social support (isolated high-strain jobs). Indeed, a**
595 **cross-sectional study in German-speaking executives conducted on 348 male and 76 female**
596 **executives and managers from Germany, Austria and Switzerland showed that lack of social support,**
597 **and job demands were related to poor sleep quality especially in females (Gadinger et al., 2009). A**
598 **similar study conducted on 1209 male workers confirmed these data highlighting independent effects**
599 **of job strain and job control on insomnia development (Nomura et al., 2009).**

600 **Burnout represents a negative affective state that comprises feelings of emotional exhaustion,**
601 **physical fatigue, and cognitive weariness, and denotes depletion of energetic resources resulting from**
602 **cumulative exposure to chronic work and chronic life stresses. There is compelling evidence, based**
603 **on both questionnaire data and objective polysomnographic recordings, pointing to an association**
604 **between burnout and sleep disturbances, particularly chronic insomnia (Ekstedt et al., 2006;**
605 **Melamed et al., 1999). Moreover, both burnout and insomnia are closely associated with chronic**

606 stress. These 3 elements seem to be chasing each other on a vicious circle. For example, insomnia
607 can cause non-refreshing sleep and waking up exhausted (Riemann et al., 2012) in individuals who
608 are also exposed to work and life stresses reducing their resources for coping with stress, thus,
609 exacerbating symptoms of mental and physical fatigue and, ultimately, sustaining burnout or the
610 development of new cases of burnout (Armon et al., 2008).

611

612 In conclusion, since many different chronic stress protocols have been used in rodent experiments
613 and many different types of stressors can be encountered in everyday life by humans, it is complicated
614 to draw a unifying picture on the effects of chronic stress on sleep architecture. This is probably due
615 to the fact that, besides the type of stressors, temporal dimension (how many times and for how long
616 a stressor has been applied?) has a critical role in the stress responses and, thus, it must be carefully
617 considered. However, a reduction in NREM sleep time seems to be a distinctive tract of chronic stress
618 exposure in humans as well as in several experimental protocols applied to rodents (Papale et al.,
619 2005).

620

621

622 **3.4. Long-term effects of early-life stress on sleep**

623 Stress responses are critically linked to temporal dynamics. For example, the exposure to a brief
624 session of inescapable and unpredictable footshock (Miller et al., 1975) has a proactive effect, and
625 the reactivity to a minor stressor increases progressively during period after the stress experience
626 (Van Dijken et al., 1992). The importance of the temporal dynamics in terms of hours, days and weeks
627 of a wide variety of stress parameters after the termination of the stressor itself has been discussed
628 several years ago by Koolhaas et al. (Koolhaas et al., 1997). At that time, little was known about the
629 mechanisms involved in these long-term effects of stress. Today, we start to unravel the cascade of
630 neurobiological processes induced by stress. Each of these processes may have a different time
631 course, ranging from milliseconds in the case of direct signal transduction processes, to minutes,
632 hours and days when modulatory processes are involved at the level of DNA transcription and peptide
633 synthesis. This cascade may lead ultimately to permanent alterations at the level of neuronal
634 morphology and fine tuning of neurochemical signal transduction mechanisms. Moreover, repeated
635 (chronic) exposure to stressors likely entails differential additive effects depending on the time
636 interval between stressors (Koolhaas et al., 1997). Considering these concepts, in this section we will
637 extend the hypothesis of the time-dependent consequences of stress response to a different (longer)
638 time scale. In particular, we will deal with the long-term effects produced by perinatal stress on sleep
639 phenotype.

640 The number of studies focusing on the possible relationship between perinatal stress exposure and
641 adult sleep derangements is rapidly increasing. As expected, due to numerous possible confounders,
642 performing these studies in humans is very complex. Thus, animal studies in which it is possible to
643 limit confounders such as genetic variability, pharmacological therapies, different lifestyles, and so
644 on, might represent a very useful tool in the understanding of the long-term effects of early-life stress.
645 Several methods to induce early-life stress have been used in animal models, either before (prenatal
646 stress) or immediately after (postnatal stress) **birth**. Applied prenatal stressors include maternal
647 restraining (Dugovic et al., 1999; Rao et al., 1999), malnutrition (Datta et al., 2000; Duran et al.,
648 2006), exposure to various stimuli (bright light (Koehl et al., 1999), or hypoxia (Joseph et al., 2002),
649 whereas cross-fostering (Santangeli et al., 2016) and, particularly, maternal separation (Feng et al.,
650 2007; Perez-Morales et al., 2014; Sampath et al., 2014; Tiba et al., 2003; Tiba et al., 2004, 2008) have
651 been used as protocols for postnatal stress.
652 In the following sections, we will discuss the long-term effects exerted by either prenatal or postnatal
653 stress on adult sleep **phenotype**. In both cases we will provide a comprehensive review of both animal
654 and human studies so far performed.

655

656 3.4.1. Prenatal Stress

657 In one of the first works exploring the relationship between prenatal stress and adult sleep phenotype
658 in rodents (Dugovic et al., 1999), pregnant rats were restrained 3 times a day during the last week of
659 gestation and then the offspring's phenotype was evaluated at 3-4 months of age. Prenatally stressed
660 rats showed sleep fragmentation, a slight decrease in NREM sleep during the active (dark) phase **and**
661 **an increased amount of REM sleep**. An increased amount of time spent in REM sleep, positively
662 correlated to plasma corticosterone levels, was found by another study, in which the authors also
663 reported a phase advance in hormonal/behavioral circadian rhythms of adult rats that had been
664 prenatally stressed (Mairesse et al., 2015). A decrease in time spent in NREM sleep, together with
665 prolonged REM sleep latency, was also described in another preliminary report using a similar stress
666 protocol (Rao et al., 1999).

667 There is evidence that protein malnutrition experienced at a time when the nervous system is
668 developing rapidly significantly impacts the development of the central nervous system and affects
669 both the circadian rhythm and homeostatic processes involved in the **wake-sleep cycle regulation**. In
670 particular, prenatal manipulations in nutritional status induce alterations in hippocampal
671 neurogenesis, as well as reduce granular cell size, dendritic complexity, and synaptic spine density.
672 When tested shortly after weaning, prenatally malnourished rats exhibited a phase shift in the
673 occurrence of both wakefulness and REM sleep, and during adulthood they showed increased levels

674 of corticosterone after restraining (Duran et al., 2006). However, discordant results have been
675 reported concerning their wake-sleep cycle alteration. In one case it was reported that prenatally
676 malnourished rats spent more time in NREM sleep and less time in REM sleep than controls (Datta
677 et al., 2000), whereas the opposite was shown in a later published study (Duran et al., 2006).

678 In another prenatal stress protocol (Koehl et al., 1999), in which pregnant rats were exposed to bright
679 light during the last week of gestation, circadian rhythmicity of the HPA axis was evaluated in adult
680 offspring. Interestingly, the authors reported that prenatal stress induced long-term changes in the
681 circadian rhythm of corticosterone secretion but not in ACTH rhythmicity. Particularly, in both males
682 and females, prenatal stress induced modifications in the temporal pattern of daily corticosterone
683 **secretion** reflected by increased levels during the light period. In females, an increased secretion of
684 corticosterone over the entire 24-h period was observed. Finally, hippocampal MRs were constantly
685 downregulated throughout the 24-h period both in male and female rats, whereas hippocampal GRs
686 were downregulated only in male rats and only during the light (resting) period.

687 Prenatal exposure of pregnant rats to hypoxia induced, in the adult offspring, marked alterations of
688 the functional organization of the circadian rhythm of activity associated with decreased sensitivity
689 of the biological clock to light. Under a regular light-dark cycle, these rats showed a phase advance
690 of the onset of activity and were less active than controls. Even this prenatal stress protocol was
691 enough to entail hyperresponsiveness of the HPA axis (i.e., increased corticosterone levels) to acute
692 restraining in the adult offspring. Thus, it is fascinating to speculate that these HPA axis
693 derangements, possibly through the modulation of clock genes (i.e., Per1-3), were responsible for the
694 altered circadian rhythmicity in this rodent model of early-life stress. Unfortunately, in this study
695 gene clock expression was not evaluated, thus leaving this hypothesis an open question.

696 Surprisingly, it has been documented that prenatal stress exposure may impact on fathers'
697 spermatogenesis and, particularly, on microRNA composition (Rodgers et al., 2015). In this case,
698 however, rats exposed to chronic stress showed a specific microRNA pattern (**Table 1**), entailing a
699 reduction in the HPA axis activity in adult offspring. Thus, contrary to what happens in the mothers,
700 perinatal stress exposure in the fathers seems to entail, through sperm microRNAs, a protective role
701 against HPA hyperactivation in the offspring. However, since this is a completely new field of
702 research, no evidence is yet available concerning the possible consequences of paternal prenatal stress
703 on offspring sleep phenotype.

704

705 As already mentioned, clinical studies exploring the link between prenatal stress and long-term
706 derangement of adult sleep **phenotype** are difficult to perform. Most human studies in this field **is**
707 predominantly descriptive and only **measures** sleep in young infants, without observing what happens

708 to them during subsequent developmental stages. Thus, in the following paragraph, we will report the
709 scientific literature highlighting long-lasting effects of prenatal stress on sleep architecture in
710 newborns.

711 Field et al. (Field et al., 2002) analyzed 106 women, dividing them into 2 groups according to their
712 anger levels during the second trimester of pregnancy. The high-anger women showed higher cortisol
713 and adrenaline and low dopamine and serotonin levels compared to low-anger pregnant women.
714 Accordingly, infants of high-anger women resulted to have higher cortisol and lower dopamine levels
715 compared to infants of low-anger women. The high-anger mothers and infants were also similar
716 regarding their relative right frontal EEG activation and their low vagal tone. Finally, the newborns
717 of high-anger mothers had disorganized sleep patterns (greater indeterminate sleep and more state
718 changes). A second study by the same group (Field et al., 2007) was performed on 253 pregnant
719 women during their second and third trimester of gestation who were assigned to depressed and non-
720 depressed groups. Depressed women self-reported more sleep disturbances, higher depression,
721 anxiety, and anger scores, and showed higher norepinephrine and cortisol urine levels than controls.
722 Newborns of depressed mothers were more active, cried more, and had more sleep disturbances,
723 including less time in deep sleep and more time in disorganized sleep. The relationship between
724 prenatal maternal anxiety/depression and sleep alteration in newborns was also investigated by two
725 more studies. The first was a large longitudinal study conducted on more than 10,000 pregnancies
726 and extended up to 30 months after delivery (O'Connor et al., 2007); the second was a study by
727 Nevarez et al. (Nevarez et al., 2010) that was performed on 1676 mother-infant pairs in a pre-birth
728 cohort study. In both these studies, the investigators found that babies of depressed pregnant women
729 were more prone to disturbed sleep with frequent nocturnal awakenings and reduced sleep duration
730 (O'Connor et al., 2007; Nevarez et al., 2010). The exact mechanism linking maternal prenatal
731 depression and infant sleep alterations has yet to be fully understood but available evidence suggests
732 that this mood condition can be considered as a sufficient psychological stress to elevate
733 glucocorticoid secretion, thus potentially perturbing fetal HPA axis activity.

734

735 Altogether, human and animal studies strongly suggest that physical and psychological stress factors
736 acting during pregnancy might have a key role in the development of long-term sleep disturbances
737 both in newborns and adults (Figure 2).

738

739

740 3.4.2. *Postnatal Stress*

741 One of the most common protocols used in animal research to evaluate the long-term effects of
742 postnatal stress is maternal separation. Of course, this protocol may vary across laboratories
743 concerning the duration of each single separation or the number of days in which the protocol was
744 applied. However, a large body of data has shown that this protocol leads to long-lasting behavioral,
745 physiological, and molecular alterations that include elevated activation of the HPA axis.
746 Behaviorally, rats which undergo maternal separation were more sensitive to stressful stimulation and
747 showed increased anxiety. Moreover, they had increased brain CRH, plasma ACTH, and
748 corticosterone both at baseline and in response to stressful stimulations (Feng et al., 2007; Plotsky et
749 al., 2005). Concerning the sleep phenotype, it has been reported that these rats had difficulty falling
750 asleep and/or difficulty staying asleep, particularly during the resting period. Indeed, they showed
751 increased total wake time and decreased total sleep time compared to controls (Feng et al., 2007;
752 Perez-Morales et al., 2014). Increased time spent in REM sleep in rats that had been maternally
753 deprived during the early-life period was also reported (Sampath et al., 2014; Tiba et al., 2004). Some
754 studies explored the sleep rebound in these adult rats after acute cold exposure or restraint,
755 highlighting that male rats showed a decrease in sleep efficiency (Tiba et al., 2003; Tiba et al., 2004)
756 whereas female rats (Tiba et al., 2008) showed an increase.
757 Finally, in a more recent rat study, changing pups between mothers at an early age (cross-fostering)
758 was used as a model of mild postnatal stress (Santangeli et al., 2016). Despite the less severe stress
759 protocol, even in this case, adult rats (both males and females) exhibited increased number of REM
760 sleep onsets during spontaneous sleep. Moreover, the total amount of time spent in REM and NREM
761 sleep during the light period was elevated in cross-fostered rats, reflected as a decrease in waking.
762 The total amount of NREM sleep was also slightly increased during the dark period (Santangeli et
763 al., 2016).

764
765 Stressful events occurring in the postnatal period or in infancy may contribute to the onset or
766 maintenance of stress system alterations even in adult humans (Davidson and McEwen, 2012; Heim
767 and Binder, 2012; Teicher et al., 2003). Several studies documented the prominent role of childhood
768 stress such as sexual, physical, or emotional abuse, emotional or physical neglect, or parental loss, in
769 the pathogenesis of stress-related disorders including mood disorders and insomnia (Carr et al., 2013;
770 Wilkinson and Goodyer, 2011). Inconsistencies in the literature (i.e., evidence of global vs. specific
771 effects) are likely to reflect several methodological differences across studies, including the
772 characteristics of the examined population (e.g., psychiatric vs. community samples; age range;
773 gender composition), the specific type of sleep disturbance assessed (e.g., trauma-related nightmares,
774 disruptive nocturnal behaviors, general sleep problems) and the type of analysis used (e.g., categorical

775 vs. continuous approaches). Despite these limitations, several studies demonstrated that exposure to
776 family conflicts or adversity during childhood must be considered risk factors and predictors for sleep
777 disorders, such as primary insomnia, later in life. (Bader et al., 2007a; Bader et al., 2007b; Bernert et
778 al., 2007; Chapman et al., 2011; Gregory et al., 2006; Noll et al., 2006). Koskenvuo et al. (Koskenvuo
779 et al., 2010) emphasized the relationship between the child-parent relationship and the poor quality
780 of sleep in a population study of 26,000 Finns. In this case, the risk of poor quality of sleep was
781 considerably increased among those with both poor relationships with parents and multiple childhood
782 adversities. Those with poor child-mother relationships and multiple adversities reported poor sleep
783 10 times more often than those with good relationships and no adversities (Koskenvuo et al., 2010).
784 Similarly, it has been shown that physical, emotional, and sexual abuse are all critical risk factors for
785 the development of sleep disturbances and poor sleep quality in adults (Bader et al., 2013; Chapman
786 et al., 2013; Greenfield et al., 2011; Ramsawh et al., 2011).

787 All these stressful events experienced during sensitive periods of development might fundamentally
788 alter the neuroendocrine system that regulates both the stress system and wake-sleep cycle, leading
789 to chronic sleep problems (Figure 2). Hypervigilance (i.e., hyperarousal) has been described to be a
790 characteristic of subjects with adverse early life experiences, and it can persist for many years and
791 may never fully remit. Hypervigilance in traumatized individuals may reflect the promptness and
792 preparation to deal with potentially negative events. In other words, it may be considered an adaptive
793 process of the organism resulting from the persistence of stress-related neurophysiologic patterns,
794 e.g., chronically elevated levels of catecholamines (Otte et al., 2005), and of HPA axis activity (Perry
795 and Pollard, 1998). Dysregulation of the HPA axis may thus be the link between adverse childhood
796 experiences and adult insomnia (Bader et al., 2013; Bader et al., 2007a; Bader et al., 2007b; Chapman
797 et al., 2013; Chapman et al., 2011; Koskenvuo et al., 2010).

798 Few studies have investigated whether gender affects the relationship between early trauma and sleep
799 disturbances (Calhoun et al., 2014; Steine et al., 2012). Early life events and adult sleep disorders in
800 women are of particular interest because females are more frequently victims of sexual abuse.
801 Consequently, females abused during childhood are more prone to develop several types of physical
802 and psychological alterations, among which sleep problems (e.g., difficulty maintaining sleep and
803 excessive daytime sleepiness) are often reported (Elliott and Briere, 1992; Hulme, 2000; Kelly, 2010;
804 Noll et al., 2006). In particular, a couple of studies (Lind et al., 2016; Noll et al., 2006) showed that
805 childhood abuse represents an important predictor of sleep disturbances up to 25-30 years after the
806 stressful event and that the occurrence of these hypnic disturbances was higher in females than in
807 males.

808

809 Altogether, human and animal studies sustain the hypothesis of the latency model. The essence of the
810 latency model is that specific biological factors (e.g., low birth weight) or developmental
811 opportunities (e.g., adequate exposure to spoken language) at critical/sensitive periods in (early) life
812 have a lifelong impact on health and well-being, regardless of subsequent life circumstances. In line
813 with this theory, most of the crucial elements of emotional control, peer social skills, and language
814 development **has** critical periods in the first five years of human **life** (Hertzman, 1999). Since early-
815 life events may entail multiple sleep disorders and disturbances later in life, the correct development
816 of the wake-sleep cycle can also be included in the latency model (Koskenvuo et al., 2010). **Therefore**,
817 sleep may be thought of as an important mediator of the association between childhood trauma and
818 poorer health outcomes.

819

820

821 **4. EPIGENETICS AS A TARGET FOR THE CURE OF LONG-TERM SLEEP** 822 **DISTURBANCES**

823 The studies **so far** discussed suggest that early-life stress can be related to the development of
824 insomnia and other sleep derangements in newborns and later in adult life (Palagini et al., 2015),
825 producing long-lasting amplifications in stress reactivity through an alteration of HPA axis activation.
826 In this respect, negative life events could activate arousal-regulating systems inducing a condition of
827 “hyperarousal” that leads to the development of sleep disturbances with an evolution to chronic
828 insomnia. As stated above, epigenetic mechanisms may have a crucial role in connecting prenatal
829 stress, HPA dysfunction, and adult phenotype alterations (Figure 2 and **Table 1**). Thus, considering
830 that the reversibility of epigenetic modifications affecting HPA axis activity (e.g., through modulation
831 of hippocampal GR expression) has been proved (Weaver et al., 2004; Weaver et al., 2005), it might
832 **be** possible to speculate that the injection of drugs acting on epigenetic machinery (epidrugs) could
833 reprimatinate the normal HPA axis activity in adults, eventually restoring a normal sleep pattern.

834 A general classification of epidrugs is to consider them as either broad reprogrammers or targeted
835 therapies. Among these, there are DNA methyltransferases (DNMT), bromodomain and extra
836 terminal (BET), and histone deacetylase (HDAC) inhibitors. These agents have wide and dramatic
837 effects on gene expression and effectively alter the epigenetic cell signature. Nowadays, potential
838 applications for epidrugs arise in cancer, cardiovascular, neurological, and metabolic diseases, which
839 tend to have complex phenotypes and epigenetic dysregulations (Naveja and Medina-Franco, 2017).
840 For instance, BET inhibitors have already been tested in preclinical studies against heart failure,
841 inflammatory processes, and HIV reactivation, with promising results. Furthermore, HDAC
842 inhibitors **showed** promising results in murine models of Alzheimer’s disease. Concerning metabolic

843 diseases, some advances have resulted from studying epigenetic targets for diabetes and obesity
844 treatments, particularly HDACs, histone acetyltransferases (HATs), DNMTs, and
845 protein arginine methyltransferase (PRMTs) (Naveja and Medina-Franco, 2017).

846 So far, no epidrugs for treatment of sleep disorders have yet been proposed or tested.

847 An alternative strategy to prevent or reduce sleep disturbances may be to reinforce the capacity to
848 regulate stress responses, specifically in expectant mothers. Some studies have already suggested to
849 adopt psychological interventions to reduce stress during pregnancy or breastfeeding time in order to
850 reduce the risk of developing psychopathology or other negative medical outcomes. Among others,
851 mindfulness-based, music, or psychological and support intervention represent strategies
852 experimentally proved to reduce stress, anxiety and depression in pregnant women (Corbijn van
853 Willenswaard et al., 2017; San Lazaro Campillo et al., 2017; Vieten et al., 2018). Unfortunately, no
854 information is currently available on possible long-term effects of these strategies on adult sleep
855 phenotype of offspring.

856

857

858 5. SUMMARY

859 Stress is an adaptative response aimed at restoring body homeostasis and facing ambient challenges.
860 The classical neuroendocrine stress response involving the activation of the HPA axis produces a
861 plethora of different physiological effects, with different interactions occurring at multiple levels.
862 Among others, the wake-sleep cycle and circadian rhythmicity are two physiological aspects that are
863 intimately linked to stress levels. Indeed, it is known that each actor of the HPA axis (CRH, ACTH
864 and cortisol) can interfere with the physiological wake-sleep cycle either directly or indirectly through
865 the modulation of endogenous circadian rhythmicity. In the present review we first reported a series
866 of studies performed on humans and rodents showing the different sleep effects exerted by each
867 component of the HPA axis and, then, we highlighted how acute or chronic HPA axis activation
868 differently modulates the wake-sleep cycle. In addition to these well-characterized aspects, a new and
869 interesting research field deals with the relationship between sleep and stress on a different (longer)
870 time scale. A growing body of evidence shows that the exposure to perinatal stress, probably through
871 epigenetic modulations, is sufficient to cause persistent sleep derangements during adult life. In light
872 of this evidence, the main message of the present review is that the complex relationship between
873 sleep and stress changes dramatically on the basis of the time scale considered and, consequently,
874 “time” should be considered as a critical factor when facing this topic.

875

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877 None

878

879 **6. REFERENCES**

880

881 Altman, J., Bayer, S.A., 1990. Migration and distribution of two populations of hippocampal granule
882 cell precursors during the perinatal and postnatal periods. *J Comp Neurol* 301, 365-381.

883 Armon, G., Shirom, A., Shapira, I., Melamed, S., 2008. On the nature of burnout-insomnia
884 relationships: a prospective study of employed adults. *J Psychosom Res* 65, 5-12.

885 Arnold, S.E., Trojanowski, J.Q., 1996. Human fetal hippocampal development: II. The neuronal
886 cytoskeleton. *J Comp Neurol* 367, 293-307.

887 Bader, K., Schafer, V., Nissen, L., Schenkel, M., 2013. Heightened beta EEG activity during nonrapid
888 eye movement sleep in primary insomnia patients with reports of childhood maltreatment. *J Clin*
889 *Neurophysiol* 30, 188-198.

890 Bader, K., Schafer, V., Schenkel, M., Nissen, L., Kuhl, H.C., Schwander, J., 2007a. Increased
891 nocturnal activity associated with adverse childhood experiences in patients with primary insomnia.
892 *J Nerv Ment Dis* 195, 588-595.

893 Bader, K., Schafer, V., Schenkel, M., Nissen, L., Schwander, J., 2007b. Adverse childhood
894 experiences associated with sleep in primary insomnia. *J Sleep Res* 16, 285-296.

895 Balsalobre, A., Brown, S.A., Marcacci, L., Tronche, F., Kellendonk, C., Reichardt, H.M., Schutz, G.,
896 Schibler, U., 2000. Resetting of circadian time in peripheral tissues by glucocorticoid signaling.
897 *Science* 289, 2344-2347.

898 Bernert, R.A., Merrill, K.A., Braithwaite, S.R., Van Orden, K.A., Joiner, T.E., Jr., 2007. Family life
899 stress and insomnia symptoms in a prospective evaluation of young adults. *J Fam Psychol* 21, 58-66.

900 Bohlhalter, S., Murck, H., Holsboer, F., Steiger, A., 1997. Cortisol enhances non-REM sleep and
901 growth hormone secretion in elderly subjects. *Neurobiol Aging* 18, 423-429.

902 Born, J., DeKloet, E.R., Wenz, H., Kern, W., Fehm, H.L., 1991. Gluco- and antimineralocorticoid
903 effects on human sleep: a role of central corticosteroid receptors. *Am J Physiol* 260, E183-188.

904 Bouyer, J.J., Vallee, M., Deminiere, J.M., Le Moal, M., Mayo, W., 1998. Reaction of sleep-
905 wakefulness cycle to stress is related to differences in hypothalamo-pituitary-adrenal axis reactivity
906 in rat. *Brain Res* 804, 114-124.

907 Bradbury, M.J., Dement, W.C., Edgar, D.M., 1998. Effects of adrenalectomy and subsequent
908 corticosterone replacement on rat sleep state and EEG power spectra. *Am J Physiol* 275, R555-565.

909 Calhoun, S.L., Fernandez-Mendoza, J., Vgontzas, A.N., Liao, D., Bixler, E.O., 2014. Prevalence of
910 insomnia symptoms in a general population sample of young children and preadolescents: gender
911 effects. *Sleep Med* 15, 91-95.

912 Carr, C.P., Martins, C.M., Stingel, A.M., Lemgruber, V.B., Juruena, M.F., 2013. The role of early
913 life stress in adult psychiatric disorders: a systematic review according to childhood trauma subtypes.
914 *J Nerv Ment Dis* 201, 1007-1020.

915 Cartwright, R.D., 1983. Rapid eye movement sleep characteristics during and after mood-disturbing
916 events. *Arch Gen Psychiatry* 40, 197-201.

917 Cartwright, R.D., Wood, E., 1991. Adjustment disorders of sleep: the sleep effects of a major stressful
918 event and its resolution. *Psychiatry Res* 39, 199-209.

919 Chang, F.C., Opp, M.R., 1998. Blockade of corticotropin-releasing hormone receptors reduces
920 spontaneous waking in the rat. *Am J Physiol* 275, R793-802.

921 Chang, F.C., Opp, M.R., 1999. Pituitary CRH receptor blockade reduces waking in the rat. *Physiol*
922 *Behav* 67, 691-696.

923 Chang, F.C., Opp, M.R., 2004. A corticotropin-releasing hormone antisense oligodeoxynucleotide
924 reduces spontaneous waking in the rat. *Regul Pept* 117, 43-52.

925 Chapman, D.P., Liu, Y., Presley-Cantrell, L.R., Edwards, V.J., Wheaton, A.G., Perry, G.S., Croft,
926 J.B., 2013. Adverse childhood experiences and frequent insufficient sleep in 5 U.S. States, 2009: a
927 retrospective cohort study. *BMC Public Health* 13, 3.

928 Chapman, D.P., Wheaton, A.G., Anda, R.F., Croft, J.B., Edwards, V.J., Liu, Y., Sturgis, S.L., Perry,
 929 G.S., 2011. Adverse childhood experiences and sleep disturbances in adults. *Sleep Med* 12, 773-779.
 930 Charmandari, E., Chrousos, G.P., Lambrou, G.I., Pavlaki, A., Koide, H., Ng, S.S., Kino, T., 2011.
 931 Peripheral CLOCK regulates target-tissue glucocorticoid receptor transcriptional activity in a
 932 circadian fashion in man. *PLoS One* 6, e25612.
 933 Chastrette, N., Cespuglio, R., Jouvet, M., 1990. Proopiomelanocortin (POMC)-derived peptides and
 934 sleep in the rat. Part 1--Hypnogenic properties of ACTH derivatives. *Neuropeptides* 15, 61-74.
 935 Chen, J., Evans, A.N., Liu, Y., Honda, M., Saavedra, J.M., Aguilera, G., 2012. Maternal deprivation
 936 in rats is associated with corticotrophin-releasing hormone (CRH) promoter hypomethylation and
 937 enhances CRH transcriptional responses to stress in adulthood. *J Neuroendocrinol* 24, 1055-1064.
 938 Chrousos, G.P., Kino, T., 2005. Intracellular glucocorticoid signaling: a formerly simple system turns
 939 stochastic. *Sci STKE* 2005, pe48.
 940 Cirulli, F., Berry, A., Alleva, E., 2003. Early disruption of the mother-infant relationship: effects on
 941 brain plasticity and implications for psychopathology. *Neurosci Biobehav Rev* 27, 73-82.
 942 Corbijn van Willenswaard, K., Lynn, F., McNeill, J., McQueen, K., Dennis, C.L., Lobel, M.,
 943 Alderdice, F., 2017. Music interventions to reduce stress and anxiety in pregnancy: a systematic
 944 review and meta-analysis. *BMC Psychiatry* 17, 271.
 945 Curie, T., Maret, S., Emmenegger, Y., Franken, P., 2015. In Vivo Imaging of the Central and
 946 Peripheral Effects of Sleep Deprivation and Suprachiasmatic Nuclei Lesion on PERIOD-2 Protein in
 947 Mice. *Sleep* 38, 1381-1394.
 948 Datta, S., Patterson, E.H., Vincitore, M., Tonkiss, J., Morgane, P.J., Galler, J.R., 2000. Prenatal
 949 protein malnourished rats show changes in sleep/wake behavior as adults. *J Sleep Res* 9, 71-79.
 950 Davidson, R.J., McEwen, B.S., 2012. Social influences on neuroplasticity: stress and interventions to
 951 promote well-being. *Nat Neurosci* 15, 689-695.
 952 De Kloet, E.R., Vreugdenhil, E., Oitzl, M.S., Joels, M., 1998. Brain corticosteroid receptor balance
 953 in health and disease. *Endocr Rev* 19, 269-301.

954 De Souza, E.B., 1987. Corticotropin-releasing factor receptors in the rat central nervous system:
 955 characterization and regional distribution. *J Neurosci* 7, 88-100.

956 Descamps, A., Cespuglio, R., 2010. Influence of aging on the sleep rebound induced by
 957 immobilization stress in the rat. *Brain Res* 1335, 14-23.

958 Dugovic, C., Maccari, S., Weibel, L., Turek, F.W., Van Reeth, O., 1999. High corticosterone levels
 959 in prenatally stressed rats predict persistent paradoxical sleep alterations. *J Neurosci* 19, 8656-8664.

960 Duran, P., Galler, J.R., Cintra, L., Tonkiss, J., 2006. Prenatal malnutrition and sleep states in adult
 961 rats: effects of restraint stress. *Physiol Behav* 89, 156-163.

962 Ekstedt, M., Soderstrom, M., Akerstedt, T., Nilsson, J., Sondergaard, H.P., Aleksander, P., 2006.
 963 Disturbed sleep and fatigue in occupational burnout. *Scand J Work Environ Health* 32, 121-131.

964 Elliott, D.M., Briere, J., 1992. Sexual abuse trauma among professional women: validating the
 965 Trauma Symptom Checklist-40 (TSC-40). *Child Abuse Negl* 16, 391-398.

966 Feng, P., Vurbic, D., Wu, Z., Strohl, K.P., 2007. Brain orexins and wake regulation in rats exposed
 967 to maternal deprivation. *Brain Res* 1154, 163-172.

968 Field, T., Diego, M., Hernandez-Reif, M., Figueiredo, B., Schanberg, S., Kuhn, C., 2007. Sleep
 969 disturbances in depressed pregnant women and their newborns. *Infant Behav Dev* 30, 127-133.

970 Field, T., Diego, M., Hernandez-Reif, M., Salman, F., Schanberg, S., Kuhn, C., Yando, R., Bendell,
 971 D., 2002. Prenatal anger effects on the fetus and neonate. *J Obstet Gynaecol* 22, 260-266.

972 Fukuoka, Y., Burioka, N., Takata, M., Ohdo, S., Miyata, M., Endo, M., Shimizu, E., 2005.
 973 Glucocorticoid administration increases hPer1 mRNA levels in human peripheral blood mononuclear
 974 cells in vitro or in vivo. *J Biol Rhythms* 20, 550-553.

975 Gadinger, M.C., Fischer, J.E., Schneider, S., Fischer, G.C., Frank, G., Kromm, W., 2009. Female
 976 executives are particularly prone to the sleep-disturbing effect of isolated high-strain jobs: a cross-
 977 sectional study in German-speaking executives. *J Sleep Res* 18, 229-237.

978 Germain, A., Buysse, D.J., Ombao, H., Kupfer, D.J., Hall, M., 2003. Psychophysiological reactivity
979 and coping styles influence the effects of acute stress exposure on rapid eye movement sleep.
980 *Psychosom Med* 65, 857-864.

981 Gildner, T.E., Liebert, M.A., Kowal, P., Chatterji, S., Snodgrass, J.J., 2014. Associations between
982 sleep duration, sleep quality, and cognitive test performance among older adults from six middle
983 income countries: results from the Study on Global Ageing and Adult Health (SAGE). *J Clin Sleep*
984 *Med* 10, 613-621.

985 Goel, N., Basner, M., Rao, H., Dinges, D.F., 2013. Circadian rhythms, sleep deprivation, and human
986 performance, *Progress in molecular biology and translational science*. Academic Press, pp. 155-190.

987 Goncharenko, A.M., 1979. Electrophysiological investigation of sleep in shift workers exposed to
988 emotional stress due to work. *Hum Physiol* 5, 468-474.

989 Gonzalez, M.M., Valatx, J.L., 1997. Effect of intracerebroventricular administration of alpha-helical
990 CRH (9-41) on the sleep/waking cycle in rats under normal conditions or after subjection to an acute
991 stressful stimulus. *J Sleep Res* 6, 164-170.

992 Greenfield, E.A., Lee, C., Friedman, E.L., Springer, K.W., 2011. Childhood abuse as a risk factor for
993 sleep problems in adulthood: evidence from a U.S. national study. *Ann Behav Med* 42, 245-256.

994 Gregory, A.M., Caspi, A., Moffitt, T.E., Poulton, R., 2006. Family conflict in childhood: a predictor
995 of later insomnia. *Sleep* 29, 1063-1067.

996 Gross, K.L., Cidlowski, J.A., 2008. Tissue-specific glucocorticoid action: a family affair. *Trends*
997 *Endocrinol Metab* 19, 331-339.

998 Heim, C., Binder, E.B., 2012. Current research trends in early life stress and depression: review of
999 human studies on sensitive periods, gene-environment interactions, and epigenetics. *Exp Neurol* 233,
1000 102-111.

1001 Held, K., Kunzel, H., Ising, M., Schmid, D.A., Zobel, A., Murck, H., Holsboer, F., Steiger, A., 2004.
1002 Treatment with the CRH1-receptor-antagonist R121919 improves sleep-EEG in patients with
1003 depression. *J Psychiatr Res* 38, 129-136.

1004 Hertzman, C., 1999. The biological embedding of early experience and its effects on health in
1005 adulthood. *Ann N Y Acad Sci* 896, 85-95.

1006 Holshoe, J.M., 2009. Antidepressants and sleep: a review. *Perspect Psychiatr Care* 45, 191-197.

1007 Hulme, P.A., 2000. Symptomatology and health care utilization of women primary care patients who
1008 experienced childhood sexual abuse. *Child Abuse Negl* 24, 1471-1484.

1009 Jacobson, L., Sapolsky, R., 1991. The role of the hippocampus in feedback regulation of the
1010 hypothalamic-pituitary-adrenocortical axis. *Endocr Rev* 12, 118-134.

1011 Johnson, J.V., Hall, E.M., Theorell, T., 1989. Combined effects of job strain and social isolation on
1012 cardiovascular disease morbidity and mortality in a random sample of the Swedish male working
1013 population. *Scand J Work Environ Health* 15, 271-279.

1014 Joseph, V., Mamet, J., Lee, F., Dalmaz, Y., Van Reeth, O., 2002. Prenatal hypoxia impairs circadian
1015 synchronisation and response of the biological clock to light in adult rats. *J Physiol* 543, 387-395.

1016 Kalmbach, D.A., Cuamatzi-Castelan, A.S., Tonnu, C.V., Tran, K.M., Anderson, J.R., Roth, T., Drake,
1017 C.L., 2018. Hyperarousal and sleep reactivity in insomnia: current insights. *Nat Sci Sleep* 10, 193-
1018 201.

1019 Kalsbeek, A., van der Spek, R., Lei, J., Endert, E., Buijs, R.M., Fliers, E., 2012. Circadian rhythms
1020 in the hypothalamo-pituitary-adrenal (HPA) axis. *Mol Cell Endocrinol* 349, 20-29.

1021 Kamphuis, J., Lancel, M., Koolhaas, J.M., Meerlo, P., 2015. Deep sleep after social stress: NREM
1022 sleep slow-wave activity is enhanced in both winners and losers of a conflict. *Brain Behav Immun*
1023 47, 149-154.

1024 Kant, G.J., Pastel, R.H., Bauman, R.A., Meininger, G.R., Maughan, K.R., Robinson, T.N., 3rd,
1025 Wright, W.L., Covington, P.S., 1995. Effects of chronic stress on sleep in rats. *Physiol Behav* 57,
1026 359-365.

1027 Karatsoreos, I.N., Bhagat, S., Bloss, E.B., Morrison, J.H., McEwen, B.S., 2011. Disruption of
1028 circadian clocks has ramifications for metabolism, brain, and behavior. *Proc Natl Acad Sci U S A*
1029 108, 1657-1662.

1030 Kecklund, G., Akerstedt, T., 2004. Apprehension of the subsequent working day is associated with a
1031 low amount of slow wave sleep. *Biol Psychol* 66, 169-176.

1032 Kelly, U., 2010. Intimate partner violence, physical health, posttraumatic stress disorder, depression,
1033 and quality of life in latinas. *West J Emerg Med* 11, 247-251.

1034 Kiessling, S., Eichele, G., Oster, H., 2010. Adrenal glucocorticoids have a key role in circadian
1035 resynchronization in a mouse model of jet lag. *J Clin Invest* 120, 2600-2609.

1036 Kim, E.J., Dimsdale, J.E., 2007. The effect of psychosocial stress on sleep: a review of
1037 polysomnographic evidence. *Behav Sleep Med* 5, 256-278.

1038 Kimura, M., Muller-Preuss, P., Lu, A., Wiesner, E., Flachskamm, C., Wurst, W., Holsboer, F.,
1039 Deussing, J.M., 2010. Conditional corticotropin-releasing hormone overexpression in the mouse
1040 forebrain enhances rapid eye movement sleep. *Mol Psychiatry* 15, 154-165.

1041 Koehl, M., Darnaudery, M., Dulluc, J., Van Reeth, O., Le Moal, M., Maccari, S., 1999. Prenatal stress
1042 alters circadian activity of hypothalamo-pituitary-adrenal axis and hippocampal corticosteroid
1043 receptors in adult rats of both gender. *J Neurobiol* 40, 302-315.

1044 Koolhaas, J.M., Meerlo, P., De Boer, S.F., Strubbe, J.H., Bohus, B., 1997. The temporal dynamics of
1045 the stress response. *Neurosci Biobehav Rev* 21, 775-782.

1046 Koranyi, L., Beyer, C., Guzman-Flores, C., 1971. Multiple unit activity during habituation, sleep-
1047 wakefulness cycle and the effect of ACTH and corticosteroid treatment. *Physiol Behav* 7, 321-329.

1048 Koskenvuo, K., Hublin, C., Partinen, M., Paunio, T., Koskenvuo, M., 2010. Childhood adversities
1049 and quality of sleep in adulthood: A population-based study of 26,000 Finns. *Sleep Med* 11, 17-22.

1050 Kwon, K.J., Lee, E.J., Kim, M.K., Jeon, S.J., Choi, Y.Y., Shin, C.Y., Han, S.H., 2015. The potential
1051 role of melatonin on sleep deprivation-induced cognitive impairments: implication of FMRP on
1052 cognitive function. *Neuroscience* 301, 403-414.

1053 Laus, M.F., Vales, L.D., Costa, T.M., Almeida, S.S., 2011. Early postnatal protein-calorie
1054 malnutrition and cognition: a review of human and animal studies. *Int J Environ Res Public Health*
1055 8, 590-612.

1056 Lehmann, J., Pryce, C.R., Feldon, J., 2000. Lack of effect of an early stressful life event on
 1057 sensorimotor gating in adult rats. *Schizophr Res* 41, 365-371.

1058 Levine, S., 2001. Primary social relationships influence the development of the hypothalamic--
 1059 pituitary--adrenal axis in the rat. *Physiol Behav* 73, 255-260.

1060 Lind, M.J., Aggen, S.H., Kendler, K.S., York, T.P., Amstadter, A.B., 2016. An epidemiologic study
 1061 of childhood sexual abuse and adult sleep disturbances. *Psychol Trauma* 8, 198-205.

1062 Loria, A.S., Ho, D.H., Pollock, J.S., 2014. A mechanistic look at the effects of adversity early in life
 1063 on cardiovascular disease risk during adulthood. *Acta Physiol (Oxf)* 210, 277-287.

1064 Lucassen, P.J., Naninck, E.F., van Goudoever, J.B., Fitzsimons, C., Joels, M., Korosi, A., 2013.
 1065 Perinatal programming of adult hippocampal structure and function; emerging roles of stress,
 1066 nutrition and epigenetics. *Trends Neurosci* 36, 621-631.

1067 Mairesse, J., Van Camp, G., Gatta, E., Marrocco, J., Reynaert, M.L., Consolazione, M., Morley-
 1068 Fletcher, S., Nicoletti, F., Maccari, S., 2015. Sleep in prenatally restraint stressed rats, a model of
 1069 mixed anxiety-depressive disorder. *Adv Neurobiol* 10, 27-44.

1070 Marinesco, S., Bonnet, C., Cespuglio, R., 1999. Influence of stress duration on the sleep rebound
 1071 induced by immobilization in the rat: a possible role for corticosterone. *Neuroscience* 92, 921-933.

1072 Matthews, P.A., Samuelsson, A.M., Seed, P., Pombo, J., Oben, J.A., Poston, L., Taylor, P.D., 2011.
 1073 Fostering in mice induces cardiovascular and metabolic dysfunction in adulthood. *J Physiol* 589,
 1074 3969-3981.

1075 McEwen, B.S., Karatsoreos, I.N., 2015. Sleep Deprivation and Circadian Disruption: Stress,
 1076 Allostasis, and Allostatic Load. *Sleep Med Clin* 10, 1-10.

1077 Meaney, M.J., 2001. Maternal care, gene expression, and the transmission of individual differences
 1078 in stress reactivity across generations. *Annu Rev Neurosci* 24, 1161-1192.

1079 Meerlo, P., de Bruin, E.A., Strijkstra, A.M., Daan, S., 2001a. A social conflict increases EEG slow-
 1080 wave activity during subsequent sleep. *Physiol Behav* 73, 331-335.

1081 Meerlo, P., Easton, A., Bergmann, B.M., Turek, F.W., 2001b. Restraint increases prolactin and REM
1082 sleep in C57BL/6J mice but not in BALB/cJ mice. *Am J Physiol Regul Integr Comp Physiol* 281,
1083 R846-854.

1084 Meerlo, P., Pragt, B.J., Daan, S., 1997. Social stress induces high intensity sleep in rats. *Neurosci Lett*
1085 225, 41-44.

1086 Meerlo, P., Sgoifo, A., De Boer, S.F., Koolhaas, J.M., 1999. Long-lasting consequences of a social
1087 conflict in rats: behavior during the interaction predicts subsequent changes in daily rhythms of heart
1088 rate, temperature, and activity. *Behav Neurosci* 113, 1283-1290.

1089 Meerlo, P., Sgoifo, A., Turek, F.W., 2002. The effects of social defeat and other stressors on the
1090 expression of circadian rhythms. *Stress* 5, 15-22.

1091 Meerlo, P., Turek, F.W., 2001. Effects of social stimuli on sleep in mice: non-rapid-eye-movement
1092 (NREM) sleep is promoted by aggressive interaction but not by sexual interaction. *Brain Res* 907,
1093 84-92.

1094 Melamed, S., Ugarten, U., Shirom, A., Kahana, L., Lerman, Y., Froom, P., 1999. Chronic burnout,
1095 somatic arousal and elevated salivary cortisol levels. *J Psychosom Res* 46, 591-598.

1096 Mellman, T.A., Bustamante, V., Fins, A.I., Pigeon, W.R., Nolan, B., 2002. REM sleep and the early
1097 development of posttraumatic stress disorder. *Am J Psychiatry* 159, 1696-1701.

1098 Miller, W.R., Seligman, M.E., Kurlander, H.M., 1975. Learned helplessness, depression, and anxiety.
1099 *J Nerv Ment Dis* 161, 347-357.

1100 Mongrain, V., Hernandez, S.A., Pradervand, S., Dorsaz, S., Curie, T., Hagiwara, G., Gip, P., Heller,
1101 H.C., Franken, P., 2010. Separating the contribution of glucocorticoids and wakefulness to the
1102 molecular and electrophysiological correlates of sleep homeostasis. *Sleep* 33, 1147-1157.

1103 Murgatroyd, C., Patchev, A.V., Wu, Y., Micale, V., Bockmuhl, Y., Fischer, D., Holsboer, F., Wotjak,
1104 C.T., Almeida, O.F., Spengler, D., 2009. Dynamic DNA methylation programs persistent adverse
1105 effects of early-life stress. *Nat Neurosci* 12, 1559-1566.

1106 Naveja, J.J., Medina-Franco, J.L., 2017. Insights from pharmacological similarity of epigenetic
1107 targets in epipolypharmacology. *Drug Discov Today*.

1108 Nevarez, M.D., Rifas-Shiman, S.L., Kleinman, K.P., Gillman, M.W., Taveras, E.M., 2010.
1109 Associations of early life risk factors with infant sleep duration. *Acad Pediatr* 10, 187-193.

1110 Noll, J.G., Trickett, P.K., Susman, E.J., Putnam, F.W., 2006. Sleep disturbances and childhood sexual
1111 abuse. *J Pediatr Psychol* 31, 469-480.

1112 Nomura, K., Nakao, M., Takeuchi, T., Yano, E., 2009. Associations of insomnia with job strain,
1113 control, and support among male Japanese workers. *Sleep Med* 10, 626-629.

1114 O'Connor, T.G., Caprariello, P., Blackmore, E.R., Gregory, A.M., Glover, V., Fleming, P., Team,
1115 A.S., 2007. Prenatal mood disturbance predicts sleep problems in infancy and toddlerhood. *Early*
1116 *Hum Dev* 83, 451-458.

1117 Ohmori, K., Nishikawa, S., Oku, K., Oida, K., Amagai, Y., Kajiwara, N., Jung, K., Matsuda, A.,
1118 Tanaka, A., Matsuda, H., 2013. Circadian rhythms and the effect of glucocorticoids on expression of
1119 the clock gene *period1* in canine peripheral blood mononuclear cells. *Vet J* 196, 402-407.

1120 Olini, N., Rothfuchs, I., Azzinnari, D., Pryce, C.R., Kurth, S., Huber, R., 2017. Chronic social stress
1121 leads to altered sleep homeostasis in mice. *Behav Brain Res* 327, 167-173.

1122 Oomen, C.A., Girardi, C.E., Cahyadi, R., Verbeek, E.C., Krugers, H., Joels, M., Lucassen, P.J., 2009.
1123 Opposite effects of early maternal deprivation on neurogenesis in male versus female rats. *PLoS One*
1124 4, e3675.

1125 Otte, C., Neylan, T.C., Pole, N., Metzler, T., Best, S., Henn-Haase, C., Yehuda, R., Marmar, C.R.,
1126 2005. Association between childhood trauma and catecholamine response to psychological stress in
1127 police academy recruits. *Biol Psychiatry* 57, 27-32.

1128 Palagini, L., Drake, C.L., Gehrman, P., Meerlo, P., Riemann, D., 2015. Early-life origin of adult
1129 insomnia: does prenatal-early-life stress play a role? *Sleep Med* 16, 446-456.

1130 Pankevich, D.E., Mueller, B.R., Brockel, B., Bale, T.L., 2009. Prenatal stress programming of
1131 offspring feeding behavior and energy balance begins early in pregnancy. *Physiol Behav* 98, 94-102.

1132 Papale, L.A., Andersen, M.L., Antunes, I.B., Alvarenga, T.A., Tufik, S., 2005. Sleep pattern in rats
1133 under different stress modalities. *Brain Res* 1060, 47-54.

1134 Pawlyk, A.C., Morrison, A.R., Ross, R.J., Brennan, F.X., 2008. Stress-induced changes in sleep in
1135 rodents: models and mechanisms. *Neurosci Biobehav Rev* 32, 99-117.

1136 Perez-Morales, M., Fajardo-Valdez, A., Mendez-Diaz, M., Ruiz-Contreras, A.E., Prospero-Garcia,
1137 O., 2014. 2-Arachidonoylglycerol into the lateral hypothalamus improves reduced sleep in adult rats
1138 subjected to maternal separation. *Neuroreport* 25, 1437-1441.

1139 Perry, B.D., Pollard, R., 1998. Homeostasis, stress, trauma, and adaptation. A neurodevelopmental
1140 view of childhood trauma. *Child Adolesc Psychiatr Clin N Am* 7, 33-51, viii.

1141 Pillar, G., Malhotra, A., Lavie, P., 2000. Post-traumatic stress disorder and sleep-what a nightmare!
1142 *Sleep Med Rev* 4, 183-200.

1143 Plotsky, P.M., Thirivikraman, K.V., Nemeroff, C.B., Caldji, C., Sharma, S., Meaney, M.J., 2005.
1144 Long-term consequences of neonatal rearing on central corticotropin-releasing factor systems in adult
1145 male rat offspring. *Neuropsychopharmacology* 30, 2192-2204.

1146 Ramsawh, H.J., Ancoli-Israel, S., Sullivan, S.G., Hitchcock, C.A., Stein, M.B., 2011. Neuroticism
1147 mediates the relationship between childhood adversity and adult sleep quality. *Behav Sleep Med* 9,
1148 130-143.

1149 Rao, U., McGinty, D.J., Shinde, A., McCracken, J.T., Poland, R.E., 1999. Prenatal stress is associated
1150 with depression-related electroencephalographic sleep changes in adult male rats: a preliminary
1151 report. *Prog Neuropsychopharmacol Biol Psychiatry* 23, 929-939.

1152 Reul, J.M., de Kloet, E.R., 1985. Two receptor systems for corticosterone in rat brain:
1153 microdistribution and differential occupation. *Endocrinology* 117, 2505-2511.

1154 Reynolds, C.F., 3rd, Hoch, C.C., Buysse, D.J., Houck, P.R., Schlermitzauer, M., Pasternak, R.E.,
1155 Frank, E., Mazumdar, S., Kupfer, D.J., 1993. Sleep after spousal bereavement: a study of recovery
1156 from stress. *Biol Psychiatry* 34, 791-797.

1157 Reynolds, R.M., 2013. Programming effects of glucocorticoids. *Clin Obstet Gynecol* 56, 602-609.

1158 Riemann, D., Nissen, C., Palagini, L., Otte, A., Perlis, M.L., Spiegelhalder, K., 2015. The
1159 neurobiology, investigation, and treatment of chronic insomnia. *Lancet Neurol* 14, 547-558.

1160 Riemann, D., Spiegelhalder, K., Feige, B., Voderholzer, U., Berger, M., Perlis, M., Nissen, C., 2010.
1161 The hyperarousal model of insomnia: a review of the concept and its evidence. *Sleep Med Rev* 14,
1162 19-31.

1163 Riemann, D., Spiegelhalder, K., Nissen, C., Hirscher, V., Baglioni, C., Feige, B., 2012. REM sleep
1164 instability--a new pathway for insomnia? *Pharmacopsychiatry* 45, 167-176.

1165 Rodgers, A.B., Morgan, C.P., Leu, N.A., Bale, T.L., 2015. Transgenerational epigenetic
1166 programming via sperm microRNA recapitulates effects of paternal stress. *Proc Natl Acad Sci U S A*
1167 112, 13699-13704.

1168 Romanowski, C.P., Fenzl, T., Flachskamm, C., Wurst, W., Holsboer, F., Deussing, J.M., Kimura, M.,
1169 2010. Central deficiency of corticotropin-releasing hormone receptor type 1 (CRH-R1) abolishes
1170 effects of CRH on NREM but not on REM sleep in mice. *Sleep* 33, 427-436.

1171 Sage, D., Ganem, J., Guillaumond, F., Laforge-Anglade, G., Francois-Bellan, A.M., Bosler, O.,
1172 Becquet, D., 2004. Influence of the corticosterone rhythm on photic entrainment of locomotor activity
1173 in rats. *J Biol Rhythms* 19, 144-156.

1174 Sampath, D., Sabitha, K.R., Hegde, P., Jayakrishnan, H.R., Kutty, B.M., Chattarji, S., Rangarajan,
1175 G., Laxmi, T.R., 2014. A study on fear memory retrieval and REM sleep in maternal separation and
1176 isolation stressed rats. *Behav Brain Res* 273, 144-154.

1177 San Lazaro Campillo, I., Meaney, S., McNamara, K., O'Donoghue, K., 2017. Psychological and
1178 support interventions to reduce levels of stress, anxiety or depression on women's subsequent
1179 pregnancy with a history of miscarriage: an empty systematic review. *BMJ Open* 7, e017802.

1180 Sanford, L.D., Fang, J., Tang, X., 2003. Sleep after differing amounts of conditioned fear training in
1181 BALB/cJ mice. *Behav Brain Res* 147, 193-202.

1182 Sanford, L.D., Silvestri, A.J., Ross, R.J., Morrison, A.R., 2001. Influence of fear conditioning on
1183 elicited ponto-geniculo-occipital waves and rapid eye movement sleep. *Arch Ital Biol* 139, 169-183.

1184 Sanford, L.D., Suchecki, D., Meerlo, P., 2015. Stress, arousal, and sleep. *Curr Top Behav Neurosci*
1185 25, 379-410.

1186 Santangeli, O., Lehtikuja, H., Palomaki, E., Wigren, H.K., Paunio, T., Porkka-Heiskanen, T., 2016.
1187 Sleep and Behavior in Cross-Fostering Rats: Developmental and Sex Aspects. *Sleep* 39, 2211-2221.

1188 Schmidt, M.V., Levine, S., Alam, S., Harbich, D., Sterlemann, V., Ganea, K., de Kloet, E.R.,
1189 Holsboer, F., Muller, M.B., 2006. Metabolic signals modulate hypothalamic-pituitary-adrenal axis
1190 activation during maternal separation of the neonatal mouse. *J Neuroendocrinol* 18, 865-874.

1191 Seckl, J.R., 2004. Prenatal glucocorticoids and long-term programming. *Eur J Endocrinol* 151 Suppl
1192 3, U49-62.

1193 Segall, L.A., Amir, S., 2010. Glucocorticoid regulation of clock gene expression in the mammalian
1194 limbic forebrain. *J Mol Neurosci* 42, 168-175.

1195 Soderstrom, M., Ekstedt, M., Akerstedt, T., Nilsson, J., Axelsson, J., 2004. Sleep and sleepiness in
1196 young individuals with high burnout scores. *Sleep* 27, 1369-1377.

1197 Son, G.H., Chung, S., Choe, H.K., Kim, H.D., Baik, S.M., Lee, H., Lee, H.W., Choi, S., Sun, W.,
1198 Kim, H., Cho, S., Lee, K.H., Kim, K., 2008. Adrenal peripheral clock controls the autonomous
1199 circadian rhythm of glucocorticoid by causing rhythmic steroid production. *Proc Natl Acad Sci U S*
1200 A 105, 20970-20975.

1201 Sotak, M., Bryndova, J., Ergang, P., Vagnerova, K., Kvapilova, P., Vodicka, M., Pacha, J., Sumova,
1202 A., 2016. Peripheral circadian clocks are diversely affected by adrenalectomy. *Chronobiol Int* 33,
1203 520-529.

1204 Spencer, S.J., 2013. Perinatal programming of neuroendocrine mechanisms connecting feeding
1205 behavior and stress. *Front Neurosci* 7, 109.

1206 Spiegel, K., Tasali, E., Penev, P., Van Cauter, E., 2004. Brief communication: Sleep curtailment in
1207 healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased
1208 hunger and appetite. *Ann Intern Med* 141, 846-850.

1209 Spielman, A.J., Caruso, L.S., Glovinsky, P.B., 1987. A behavioral perspective on insomnia treatment.
1210 Psychiatr Clin North Am 10, 541-553.

1211 Steiger, A., 2007. Neurochemical regulation of sleep. J Psychiatr Res 41, 537-552.

1212 Steiger, A., Dresler, M., Kluge, M., Schussler, P., 2013. Pathology of sleep, hormones and depression.
1213 Pharmacopsychiatry 46 Suppl 1, S30-35.

1214 Steiger, A., Guldner, J., Knisatschek, H., Rothe, B., Lauer, C., Holsboer, F., 1991. Effects of an
1215 ACTH/MSH(4-9) analog (HOE 427) on the sleep EEG and nocturnal hormonal secretion in humans.
1216 Peptides 12, 1007-1010.

1217 Steine, I.M., Harvey, A.G., Krystal, J.H., Milde, A.M., Gronli, J., Bjorvatn, B., Nordhus, I.H., Eid,
1218 J., Pallesen, S., 2012. Sleep disturbances in sexual abuse victims: a systematic review. Sleep Med
1219 Rev 16, 15-25.

1220 Swerdlow, N.R., Geyer, M.A., Vale, W.W., Koob, G.F., 1986. Corticotropin-releasing factor
1221 potentiates acoustic startle in rats: blockade by chlordiazepoxide. Psychopharmacology (Berl) 88,
1222 147-152.

1223 Takahashi, J.S., Hong, H.K., Ko, C.H., McDearmon, E.L., 2008. The genetics of mammalian
1224 circadian order and disorder: implications for physiology and disease. Nat Rev Genet 9, 764-775.

1225 Teicher, M.H., Andersen, S.L., Polcari, A., Anderson, C.M., Navalta, C.P., Kim, D.M., 2003. The
1226 neurobiological consequences of early stress and childhood maltreatment. Neurosci Biobehav Rev
1227 27, 33-44.

1228 Tiba, P.A., Palma, B.D., Tufik, S., Suchecki, D., 2003. Effects of early handling on basal and stress-
1229 induced sleep parameters in rats. Brain Res 975, 158-166.

1230 Tiba, P.A., Tufik, S., Suchecki, D., 2004. Effects of maternal separation on baseline sleep and cold
1231 stress-induced sleep rebound in adult Wistar rats. Sleep 27, 1146-1153.

1232 Tiba, P.A., Tufik, S., Suchecki, D., 2008. Long lasting alteration in REM sleep of female rats
1233 submitted to long maternal separation. Physiol Behav 93, 444-452.

1234 Tobaldini, E., Costantino, G., Solbiati, M., Cogliati, C., Kara, T., Nobili, L., Montano, N., 2017.
 1235 Sleep, sleep deprivation, autonomic nervous system and cardiovascular diseases. *Neurosci Biobehav*
 1236 *Rev* 74, 321-329.
 1237 Tononi, G., Cirelli, C., 2006. Sleep function and synaptic homeostasis. *Sleep Med Rev* 10, 49-62.
 1238 Tsutsui, R., Shinomiya, K., Sendo, T., Kitamura, Y., Kamei, C., 2015. Effects of the 5-HT(1A)
 1239 Receptor Agonist Tansospirone on ACTH-Induced Sleep Disturbance in Rats. *Biol Pharm Bull* 38,
 1240 884-888.
 1241 Van Cauter, E., Tasali, E., 2017. Endocrine physiology in relation to sleep and sleep disturbances, in:
 1242 Kryger, M., Roth, T., Dement, W.C. (Eds.), *Principles and practice of sleep medicine*. Elsevier,
 1243 Philadelphia, PA, pp. 202-219.
 1244 Van Dijken, H.H., Van der Heyden, J.A., Mos, J., Tilders, F.J., 1992. Inescapable footshocks induce
 1245 progressive and long-lasting behavioural changes in male rats. *Physiol Behav* 51, 787-794.
 1246 van Oers, H.J., de Kloet, E.R., Levine, S., 1999. Persistent effects of maternal deprivation on HPA
 1247 regulation can be reversed by feeding and stroking, but not by dexamethasone. *J Neuroendocrinol* 11,
 1248 581-588.
 1249 Vazquez-Palacios, G., Retana-Marquez, S., Bonilla-Jaime, H., Velazquez-Moctezuma, J., 2001.
 1250 Further definition of the effect of corticosterone on the sleep-wake pattern in the male rat. *Pharmacol*
 1251 *Biochem Behav* 70, 305-310.
 1252 Veldhuis, H.D., Van Koppen, C., Van Ittersum, M., De Kloet, E.R., 1982. Specificity of the adrenal
 1253 steroid receptor system in rat hippocampus. *Endocrinology* 110, 2044-2051.
 1254 Vgontzas, A.N., Zoumakis, E., Bixler, E.O., Lin, H.M., Follett, H., Kales, A., Chrousos, G.P., 2004.
 1255 Adverse effects of modest sleep restriction on sleepiness, performance, and inflammatory cytokines.
 1256 *J Clin Endocrinol Metab* 89, 2119-2126.
 1257 Vieten, C., Laraia, B.A., Kristeller, J., Adler, N., Coleman-Phox, K., Bush, N.R., Wahbeh, H.,
 1258 Duncan, L.G., Epel, E., 2018. The mindful moms training: development of a mindfulness-based
 1259 intervention to reduce stress and overeating during pregnancy. *BMC Pregnancy Childbirth* 18, 201.

1260 Weaver, I.C., Cervoni, N., Champagne, F.A., D'Alessio, A.C., Sharma, S., Seckl, J.R., Dymov, S.,
 1261 Szyf, M., Meaney, M.J., 2004. Epigenetic programming by maternal behavior. *Nat Neurosci* 7, 847-
 1262 854.

1263 Weaver, I.C., Champagne, F.A., Brown, S.E., Dymov, S., Sharma, S., Meaney, M.J., Szyf, M., 2005.
 1264 Reversal of maternal programming of stress responses in adult offspring through methyl
 1265 supplementation: altering epigenetic marking later in life. *J Neurosci* 25, 11045-11054.

1266 Wells, A.M., Ridener, E., Bourbonais, C.A., Kim, W., Pantazopoulos, H., Carroll, F.I., Kim, K.S.,
 1267 Cohen, B.M., Carlezon, W.A., Jr., 2017. Effects of Chronic Social Defeat Stress on Sleep and
 1268 Circadian Rhythms Are Mitigated by Kappa-Opioid Receptor Antagonism. *J Neurosci* 37, 7656-
 1269 7668.

1270 Wilkinson, P.O., Goodyer, I.M., 2011. Childhood adversity and allostatic overload of the
 1271 hypothalamic-pituitary-adrenal axis: a vulnerability model for depressive disorders. *Dev*
 1272 *Psychopathol* 23, 1017-1037.

1273 Wu, H., Dunnett, S., Ho, Y.S., Chang, R.C., 2019. The role of sleep deprivation and circadian rhythm
 1274 disruption as risk factors of Alzheimer's disease. *Front Neuroendocrinol*, 100764.

1275 Yaffe, K., Laffan, A.M., Harrison, S.L., Redline, S., Spira, A.P., Ensrud, K.E., Ancoli-Israel, S.,
 1276 Stone, K.L., 2011. Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and
 1277 dementia in older women. *JAMA* 306, 613-619.

1278 Yamamoto, T., Nakahata, Y., Tanaka, M., Yoshida, M., Soma, H., Shinohara, K., Yasuda, A.,
 1279 Mamine, T., Takumi, T., 2005. Acute physical stress elevates mouse period1 mRNA expression in
 1280 mouse peripheral tissues via a glucocorticoid-responsive element. *J Biol Chem* 280, 42036-42043.

1281 Yurtsever, T., Schilling, T.M., Kolsch, M., Turner, J.D., Meyer, J., Schachinger, H., Schote, A.B.,
 1282 2016. The acute and temporary modulation of PERIOD genes by hydrocortisone in healthy subjects.
 1283 *Chronobiol Int* 33, 1222-1234.

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FIGURE CAPTIONS

Figure 1. Effects of perinatal stress on development and activity of the hypothalamic-pituitary-adrenal axis. (NO COLOR)

The diagram highlights the link between early-life stress exposure (in utero life and lactation period) and the developmental alteration of the hypothalamic-pituitary-adrenal (HPA) axis in newborns. The most interesting hypothesis about this relationship is that increased maternal cortisol levels produce downregulation of glucocorticoid receptors (GRs) in the infant hippocampus. The persistent low level of GRs in the stressed hippocampus limits the physiological negative feedback role (thin dotted line) that this brain structure exerts on the HPA axis. **Because of** this interrupted negative feedback regulation, the HPA axis of newborns that have been perinatally exposed to stress results persistently hyperactivated and the level of circulating cortisol is abnormally elevated.

Figure 2. Early-life stress exposure and adult sleep disorders. (NO COLOR)

Graphical representation of the hypothesis linking perinatal (in utero life and lactation period) stress exposure to sleep disorders in adult life. According to available data, one possible explanation for these long-term effects of stress is that perinatal stress, through the epigenetic downregulation of glucocorticoid receptors (GRs) in the newborn hippocampus, deregulates the hypothalamic-pituitary-adrenal (HPA) axis activity (Figure 1). The epigenetic modulation of hippocampal GRs and, consequently, the HPA axis alteration may persist until adulthood thus predisposing the subject to develop sleep disorders such as insomnia.

Table 1. Epigenetic inheritance systems

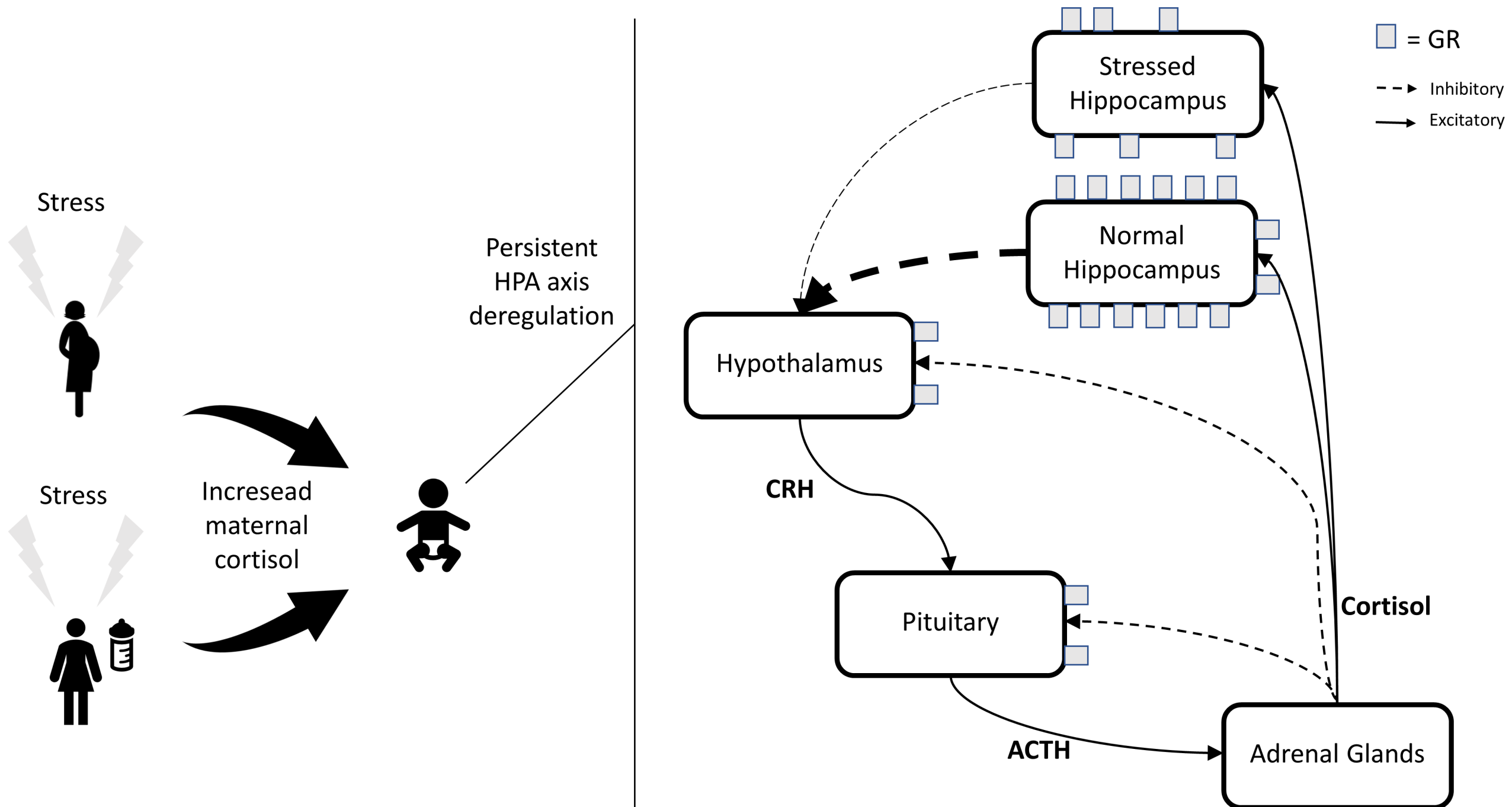
Mechanisms	Level of Action	Way of Action
DNA Methylation and Demethylation	Chromatin Remodelling	Addition or Removal of Methyl (CH ₃) groups to specific DNA sites. The DNA methylation (or demethylation) increases (or decreases) gene expression
Histon Acetylation and Deacetylation	Chromatin Remodelling	Addition or Removal of acetyl (COCH ₃) groups to histons. Histon deacetylation (or acetylation) decreases (or increases) gene expression through DNA rolling (or unrolling)
Non-Coding RNAs (such as miRNA and siRNA)	Chromatin Remodelling + Post-Transcriptional Level	Direct modulation of proteins involved in DNA (de)methylation and histon (de)acetylation systems <i>or</i> Downregulation of gene expression inhibiting specific complementary mRNA

The table shows a brief description of the level and way of action of the main epigenetic mechanisms modulating gene expression in human and rodent cells.

Table 2. Effect of hypothalamic-pituitary-adrenal axis mediators on the wake-sleep cycle.

Substance	Species	Wakefulness	NREM sleep	REM sleep
CRH	<i>Humans</i>	↑	↓	↑
	<i>Rodents</i>	↑	↓	↓
ACTH	<i>Humans</i>	↑	↓	=
	<i>Rodents, Cats and Rabbits</i>	↑	↓	↓
CORTISOL / CORTICOSTERONE	<i>Humans</i>	=	↑	↓
	<i>Rodents</i>	↑↓	↓	=

The table summarizes the effect (increased, decreased or unchanged amount, respectively ↑, ↓, =) on wakefulness, non-rapid-eye-movement (NREM) and rapid-eye-movement (REM) sleep exerted by corticotropin releasing hormone (CRH), adrenocorticotropin hormone (ACTH) and cortisol (or corticosterone for rodents).



Perinatal
Stress



Epigenetic
Downregulation of
Hippocampal GR



Persistent HPA Axis
Deregulation

Sleep Disorders

