Sleep Medicine Reviews 51 (2020) 101277

Contents lists available at ScienceDirect

Sleep Medicine Reviews

journal homepage: www.elsevier.com/locate/smrv

THEORETICAL REVIEW

Failure of fear extinction in insomnia: An evolutionary perspective

Lampros Perogamvros [a, b, c, d, *], Anna Castelnovo [e, f], David Samson [g], Thien Thanh Dang-Vu [h, i]

[a] Division of Pulmonology, Department of Medicine, Geneva University Hospitals, Geneva, Switzerland
[b] Department of Basic Neurosciences, Faculty of Medicine, University of Geneva, Geneva, Switzerland
[c] Swiss Center for Affective Sciences, University of Geneva, Geneva, Switzerland
[d] Department of Psychiatry, Geneva University Hospitals, Geneva, Switzerland
[e] Sleep Center, Neurocenter of Southern Switzerland, Civic Hospital of Lugano, Lugano, Switzerland
[f] Faculty of Biomedical Sciences, Università Della Svizzera Italiana, Lugano, Switzerland
[g] Department of Anthropology, University of Toronto, Mississauga, Canada
[h] Department of Health, Kinesiology and Applied Physiology, Perform Center and Center for Studies in Behavioral Neurobiology (CSBN), Concordia University, Montreal, Canada
[i] Centre de Recherche de L'Institut Universitaire de Gériatrie de Montréal (CRIUGM), CIUSSS Centre-Sud-de-l'île-de-Montréal, Montreal, Canada

ARTICLE INFO

Article history:
Received 19 December 2018
Received in revised form
7 January 2020
Accepted 13 January 2020
Available online 13 February 2020

Keywords:
Insomnia
Evolution
Fear extinction
Hyperarousal

SUMMARY

The pathophysiology of insomnia remains poorly understood, yet emerging cross-disciplinary approaches integrating natural history, observational studies in traditional populations, gene-phenotype expression and experiments are opening up new avenues to investigate the evolutionary origins of sleep disorders, with the potential to inform innovations in treatment. Previous authors have supported that acute insomnia is a normal biopsychosocial response to a perceived or real threat and may thus represent an adaptive response to stress. We further extend this hypothesis by claiming that insomnia reflects a fear-related evolutionary survival mechanism, which becomes persistent in some vulnerable individuals due to failure of the fear extinction function. Possible treatments targeting fear extinction are proposed, such as pharmacotherapy and emotion-based cognitive behavioral therapy.

To sleep is to distract oneself away from the universe, and this distraction is not easy when being chased with swords drawn out.

Jorge Luis Borges, The Aleph and Other Stories, 1949

Introduction

Insomnia is defined as a subjective complaint of difficulty in falling or staying asleep despite having the opportunity to do so [1]. The pathophysiology of insomnia both in its acute (<1 mo of symptoms) and chronic (>3 ms of symptoms) phase remains poorly understood. Genetic factors [2], personality traits [3], which are also largely genetically determined [4], and stressful environmental events, have been associated with insomnia, but their specific definition and role in the development and maintenance of insomnia need further investigation.

On average, every y, over one third of the adult population experiences three or more nights of insomnia (for two or more wks) [1,5,6]. In other words, up to 100% of individuals worldwide experience acute insomnia over a period of 2–3 ys. The near universality of acute insomnia supports the idea that it may be a normal, if not adaptive, aspect of human functioning. Under an evolutionary perspective, "*we live with insomnia today because at some point in our evolutionary history, insomnia allowed us to live*" (Dean Handley, Sepracor, circa 2005, cited in [7]). According to this interpretation, acute insomnia may be seen as a physiological response to acute stressors or "threats" [7–11], reflecting the ability of the organism to override and delay the more basic circadian and homeostatic drives in case of danger. In addition, new operational criteria for acute insomnia have been proposed [7], including a more graded temporal scale of symptom duration (from acute insomnia – 3–14 ds to transient - 2–4 wks, and subchronic insomnia - 1–3 ms) [7], which helps to observe insomnia under the perspective of a continuum between normal, physiological symptoms to more distressing, pathological conditions.

* Corresponding author. Department of Medicine (Geneva University Hospitals), Department of Basic Neurosciences (University of Geneva), Chemin des Mines 9, 1202, Geneva, Switzerland.
E-mail address: lampros.perogamvros@unige.ch (L. Perogamvros).

https://doi.org/10.1016/j.smrv.2020.101277
1087-0792/

Abbreviations

ACC	anterior cingulate cortex
CB1	cannabinoid receptor type 1
CBT	cognitive behavioral therapy
CBT-I	cognitive behavioral therapy for insomnia
CR	conditioned response
CS	conditioned stimulus
DSM5	Diagnostic and statistical manual of mental disorders- fifth edition
EEG	electroencephalography
ICSD	International classification of sleep disorders
NREM	non-rapid eye movement sleep
REM	rapid eye movement sleep
UR	unconditioned response
US	unconditioned stimulus
VLPO	ventrolateral preoptic nucleus
vmPFC	ventromedial prefrontal cortex

Glossary of terms

Fear conditioning	the pairing of a previously neutral stimulus with an innately aversive reinforcer (e.g., shock or loud noise), a procedure which comes to elicit a conditioned fear response.
Fear extinction	when a neutral conditioned stimulus that previously predicted an aversive unconditioned stimulus no longer does so, and the conditioned response subsequently decreases.
Evolutionary mismatch	specific traits that were once advantageous for human survival, became maladaptive due to changes in the environment.

Importantly, only some individuals satisfy international insomnia disorder criteria [5,12] on a recurrent or chronic basis. Specifically, of the 35–50% of subjects suffering from insomnia symptoms in the Western World [1,5], approximately 50% (~10–20%) face a chronic course of the disease [1,5], lasting three or more ms (and usually ys) according to both ICSD-3 and DSM-5 [5,12]. Contrary to the transient character of acute insomnia, chronic insomnia seems to become a maladaptive and pathological process where hyperarousal [13] becomes self-perpetuating, even in the absence of the initial signals of danger. Although several longitudinal or natural history studies of insomnia have been conducted [14–17], more studies of this type are needed in order to uncover the main determinants underlying the transition from transient symptoms to a persistent disorder. Several theories have tried to explain the transition from acute to chronic insomnia [18,19]. Most models support the idea that behaviors and cognitions adopted by the individuals to cope with acute insomnia, actually reinforce the problem and produce chronic insomnia, mainly by instrumental conditioning [20].

In this review, the idea of the evolutionary function of insomnia will be further investigated. We propose a fear-related *survival* mechanism underlying the origin of insomnia. As fear is a key emotional component of survival by giving rise to appropriate behavioral responses, it has been preserved throughout evolution [21]. It is here proposed that in both small-scale societies (i.e., where the product of adult work is not money, but food) and large scale agricultural and economically developed societies, several real or perceived stressors give rise to acute insomnia symptoms through fear induction and the stress response. The proposed model also predicts that wakefulness/hyperarousal in chronic insomnia is maintained through *fear conditioning* – that is, the pairing of a previously neutral stimulus (conditioned stimulus, CS) with an innately aversive reinforcer (unconditioned stimulus, US), ultimately eliciting a conditioned fear response (CR) [22,23]. In the context of insomnia, this conditioning refers to the induction of wakefulness (CR) in response to any CS that was once a neutral stimulus [24], such as the bed, bedtime, place (neighborhood), clock watching, darkness or any thought or mental image, and which was associated with the initial stressor (US). *Fear extinction* will take place when the CS that previously predicted the US no longer does so, and the CR (arousal in this case) subsequently decreases [22,25], permitting normal sleep. We propose that the failure of fear extinction and of return to safety would account for the persistent phase of insomnia and hyperarousal in some individuals (chronic insomnia). Thus, we postulate that targeting dysfunctional conditioned threat memories (i.e., CS-US associations) [26–28] would be important for a successful treatment of insomnia.

The adaptive function of acute insomnia

According to evolutionary mismatch theory, specific traits that were once advantageous for human survival became maladaptive due to changes in the environment resulting in gene-environment mismatch [29]. In other words, humans have evolved for how things were, not how things are. This hypothesis has been used to describe the occurrence and perpetuation of some medical diseases [30]. For example, obesity has often been examined from an environmental mismatch perspective. Low metabolic rates and the tendency to accumulate body fat would have been evolutionarily favorable for Paleolithic hunter-gatherers, for whom food was not always easily available. However, this advantage has progressively lost its attributes and became a pathology in societies where access to food is steady. Insomnia can also be viewed under the lens of evolutionary mismatch, as it seems to originally reflect an adaptive response to real or perceived stressors and threats that automatically activate 'fight or flight' systems and are related to the emotion of fear. Threat-related experiences (real or perceived) seem to be at the origin of many acute forms of insomnia in both the distant past and present of human history, while failure to extinguish this threat would account, at least partly, for its maladaptive persistence over time. According to evolutionary mismatch, initially adaptive

solutions from our ancestral past and their modern 'homologues', would automatically activate the same 'fight or flight' systems.

Previous authors support this view. Spielman and Glovinsky state "*No matter how important sleep may be, it was adaptively deferred when the mountain lion entered the cave*" [8]. For McNamara and Auerbach, insomnia is also an adaptive response to a perceived or real threat [9]. Ellis and colleagues suggested that acute insomnia is a normal biopsychosocial response to a perceived or actual stressor [7]. According to this hypothesis, everyone is at risk for acute insomnia as long as insomnia represents an adaptive response to stress (i.e., a real or perceived threat prevents the inhibition of wakefulness). This idea is also found in the Cano-Saper rodent model (see section 'Physiological evidence for adaptive insomnia').

Evolutionary anthropology and sociology: evidence for adaptive insomnia

Among mammals, sleep duration correlates negatively with predation risk, foraging and social interactions [31], implying that trophic level and ecology, and not functional benefits of sleep, are the primary drivers of sleep duration [11]. The patterns emerging from studies of small-scale societies indicate a mean of total sleep duration of 7.0 h within a 24 h period [32]; yet, when the sleep is timed within the circadian period, it appears to be expressed flexibly in response to ecological pressure [33,34]. A recent study in Hadza hunter-gatherers of Tanzania [33] shows that a chronotype variation – driven primarily by demographic diversity in age inherent in forager bands – and the resulting asynchrony in activity levels allow one or more individuals to stay awake during the night. In this study it was demonstrated that in 99.8% of the nighttime period at least one individual adult was awake, with a median value of eight individuals awake at any given epoch (min) during the sleep period. This naturally 'sentinalized' sleep environment would have enhanced group level survival by way of social niche construction that provided protection from environmental dangers [33]. Importantly, when surveyed for the fear stimuli (asked to rank, from greatest to least threatening, the sleep period threats within their environment), the Hadza's top two sleep-related fears are both people and animals (84.2%) and second is lack of food (65.8%) (Samson, *unpublished data*). This data demonstrates that biotic forces in the environment are primed as relevant to survival in populations that occupy a niche that resembles those of early humans, and may explain why they are characterized by shorter sleep duration, lower sleep quality, and greater levels of sleep fragmentation than humans sleeping in economically developed nations [34].

The strong links between environmental dangers, fear and acute insomnia were present not only in ancestral populations or small-scale subsistence societies, but also in modern, economically developed societies. Studies in both Western and non-Western countries demonstrate that sleep quality and insomnia symptoms are strongly associated with perceived safety from crime and violence in one's neighborhood or country [35,36], with people living in more dangerous neighborhoods (i.e., environments where the emotion of fear predominates) having considerably poorer sleep quality than those living in safer environments. Specifically, when controlling for age, gender, education, employment and income, perceived neighborhood safety, as rated on a scale from 0 (not safe at all) to 5 (completely safe) was consistently associated with reduction in the odds of insomnia symptoms in five countries Mexico, Ghana, India, China, Russia [35]. Moreover, sleep-onset insomnia is strongly associated with female gender, being black/African American, lower education attainment, lack of insurance, and food insecurity [37]. The effect of food insecurity was the largest in magnitude in predicting sleep symptoms, with an impact on sleep over and above the effects of any measured sociodemographic/socioeconomic variable [37,38]. This finding highlights the universality and strong positive correlation of food insecurity and acute insomnia symptoms in both our ancestors and modern societies. Poor sleep quality is also strongly associated with poverty and race, with employment, education and health status significantly mediating this effect only in poor subjects [39].

Under an evolutionary perspective, sleep-maintenance insomnia and early morning awakening seem to have similar threat-related origins and adaptive function with sleep-onset insomnia, as they have been strongly associated with food insecurity [37]. This variable was measured by assessing likelihood of running out of food, inability to afford food, inability to provide adequate food for children and similar items [37]. Besides, external threats may occur any time of the night. As the Australian anthropologist George B. Silberbauer reported about the G/wi hunter-gatherers of southern Africa [40]: "*A G/wi camp never has an uninterrupted night's sleep. There is always someone awake, adding wood to the household fire, eating a snack, listening to a strange noise in the bush, or keeping watch if dangerous animals are near. For this reason, the divisions of the night are almost as important as those of the day.*"

Another clear example of this is with Malagasy small-scale agriculturalists (Fig. 1), who exhibit a clear first and second sleep pattern in response to the need to work fields during the morning and evening, and buffer peak thermodynamic stress during the noon period by napping [41]. Therefore, sleep patterns can be adapted not only according to the potential presence of threats, but to social and biological functions too (Samson; *personal communication*). Another intriguing example of this is when social and cultural practices spur night–time activity, such as the *epeme* dance of the Hadza foragers, which occurs only during monthly times with the smallest lunar phase [42] (Fig. 1).

Physiological evidence for adaptive insomnia

Although the vast majority of literature on hyperarousal pertains to chronic insomnia, growing evidence from psychophysiology and neurophysiology studies offers substantial support to the presence of increased levels of arousal in acute insomnia. There are few EEG studies of stress-induced acute insomnia. In a cage-exchange paradigm [45], male rats were placed in a cage recently vacated by another male rat; the odor of the other male was perceived as threatening and stressful. A period of "acute insomnia" was observed 5–6 h after the stressor and was characterized by increased wakefulness and high-frequency EEG power during NREM sleep compared to controls [45]. Increased high frequencies in the gamma band [46] and decreased low frequencies in the delta band [47] were also found in humans when sleeping in a novel and potentially insecure environment (first-night effect) [46,47], and may reflect the ability to maintain multisensory functional integration and motor coordination if needed, as in case of a danger (night watch). In addition, transient insomnia due to the first-night effect or previous to school examinations has been related with increased skin conductance response and heart rate during all sleep stages [48,49]. The aforementioned findings support a higher baseline sympathetic activity in these individuals than in controls (physiological and cortical hyperarousal), although not as high as during maximum stress such as major surgery or intravenous administration of 50 mg hydrocortisone [50,51]. These findings suggest that these individuals are hypervigilant under certain stressful circumstances, with elevated motor readiness and 'fight-or-flight' responses. Future studies are needed in order to establish if cortical hyperarousal characterizes both chronic and acute insomnia [19,52,53].

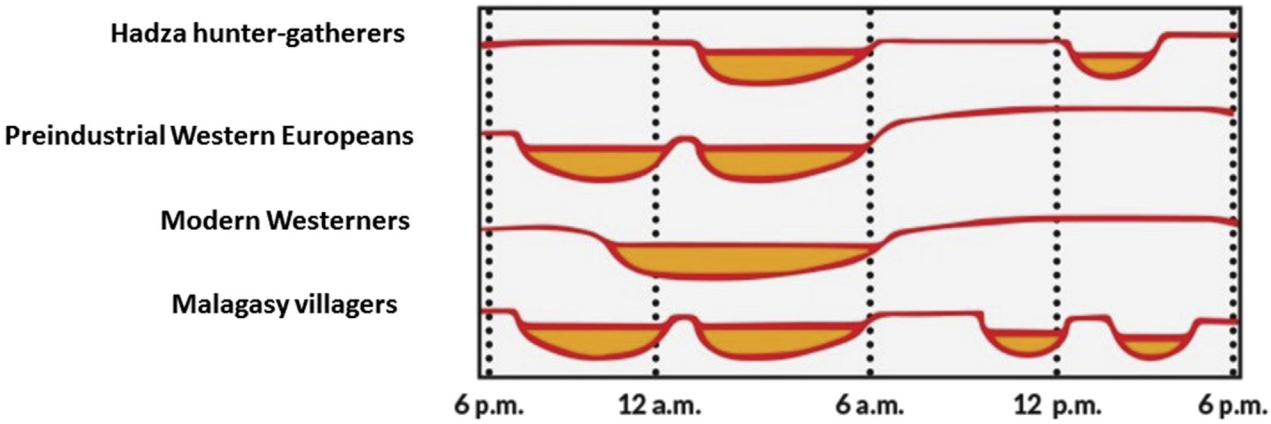

Fig. 1. Flexible sleep expression across cultures. The timing of the primary and supplementary sleep patterns in humans is variable across cultures. For example, the Hadza hunter-gatherers are characterized by a monophasic nocturnal sleep pattern illustrated by a primary, early morning bout with supplemental daytime napping. Preindustrial, European agricultural societies are characterized by a biphasic, "first sleep, second sleep" [43]. Postindustrial economies with societal demands on activity from "9 am to 5 pm," and non-work related evening activity show a monophasic pattern [44]. A small-scale, non-electric agricultural society in Madagascar shows a bifurcated pattern of nocturnal sleep bouts with supplemental daytime napping [41]. Image adapted from [34].

Interestingly, this hyperarousal in acute insomnia follows the well-known sleep-wake switch model by Saper et al. [54], in which the authors recognized the role of cognitive/emotional inputs, like stress, in shaping the interplay between sleep and wakefulness, and the dynamics between the circadian and homeostatic drives. The same authors also subsequently recognized the role of physiological inputs [55], like hunger, pain and autonomic signals, and found direct connections between centers regulating these physiological processes and the ventrolateral preoptic nucleus (VLPO), the main sleep-promoting center [56].

In sum, physiological (e.g., hunger, pain) and cognitive/emotional inputs (e.g., stress and fear because of external threats) can lead to hyperarousal, what would ultimately contribute to increased fitness benefits for the organism. This ability to override and delay the more basic circadian and homeostatic drives potentially has an adaptive function allowing individuals to continue being aware of dangers within their environment. Indeed, it was vital for our ancestors to be able to fully wake-up or postpone sleep in face of predators or a hostile conspecific.

Does acute insomnia retain adaptive function in modern environments?

The evidence from evolutionary, sociological and physiological studies supports the idea that acute insomnia reflects an increased ecological pressure and is a result of a natural process signaling that activity is preferred over sleep. Accordingly, acute insomnia may have offered increased fitness benefits for our ancestors at the presence of an external threat (e.g., defending oneself or the group against predators and hostile conspecifics or mother-infant care). During the instance of threat initiation, acute insomnia would activate global hypervigilance in order to bring the individual to a more threat-prepared state.

Throughout human history, the nature of threats causing sleeplessness (acute insomnia) has considerably changed. In our ancestral past, threats were predominantly real/actual (e.g., predators and hostile conspecifics), whereas now they are predominantly perceived/anticipated (e.g., anxiety). At the presence of a real external threat (e.g., crime, war zones) [35,36], acute insomnia remains as functional as it used to be, but would lose such function when a threat is not immediate or real, such as in anxious individuals. Indeed, considering the high prevalence of insomnia symptoms in western countries (>20% of the general population [57–59]), which – relative to our ancestral environments – are characterized by increased safety and low crime/war incidence, it seems that acute insomnia has largely lost the adaptive function it used to have. For example, in a recent study comparing sleep complaints between several developed/developing countries in Africa and Asia, South Africa, the wealthiest country had as high prevalence of sleep problems as Bangladesh, the second poorest country in the study [60]. In the absence of immediate threats and in situations where sleep is sought by the subject, acute insomnia manifests in maladaptive behaviours.

Why insomnia symptoms are so common in modern western societies, if an immediate danger from the external environment is not an issue anymore? The answer probably resides on the fact that modern societies have to face other types of threats. These threats, like those connected to our social life - ostracism and exclusion, loss of status, shame, failure in an exam etc – require actions (or reactions) that are delayed in time. Staying awake may become counterproductive instead of being an advantage, and could lead to a vicious cycle and increase stress levels due to sleep deprivation. Moreover, our brain evolved and adapted to be able to foresee potential dangers in an uncertain future. This might reduce risk-taking behaviors, but at the same time may be a disadvantage if the anticipation of danger prevents sleep.

Other sources of acute insomnia are related to rearing offspring and parent-child attachment. First, a common evolutionary reason of acute and chronic insomnia in parents as observed in the clinical practice is the need for parents to stay awake throughout the night to take care of infants. Second, the occurrence of frequent arousals is strongly associated with separation anxiety of the child and insecure parent-child attachment [61]. Such an insecure attachment decreases the child's ability to fall asleep alone and return to sleep if an arousal takes place without signalling it to the parents.

Thus, chronic insomnia seems to reflect a pathological process where hyperarousal becomes self-perpetuating (via conditioning), even in the absence of the initial threat. In the framework of our evolutionary-emotional hypothesis, this translates into a failure of the fear extinction processes, with no decline in conditioned fear

responses throughout time in certain vulnerable individuals (see later section).

The maladaptive nature of chronic insomnia

If fear-related, fight-or-flight responses are at the origin of many acute forms of insomnia, its perpetuation or remission should also be related to the preservation or extinction respectively of stimuli that maintain wakefulness over time. Following from our hypothesis, the model would place fear extinction processes (and their deficit) at the core of the physiopathology of the transition between acute and persistent forms of insomnia.

Fear conditioning and fear extinction

In general, fear conditioning refers to the pairing of a previously neutral stimulus (conditioned stimulus-CS) with an innately aversive reinforcer (e.g., shock or loud noise) (unconditioned stimulus-US), a procedure that elicits a conditioned fear response (CR) [23]. Fear conditioning is subserved by the lateral nucleus of the amygdala, which encodes the association between the CS and the US, and, via projections to the central nucleus of the amygdala, anterior cingulate cortex (ACC) and insula, controls the expression of the CR [62]. Fear conditioning is rapidly formed in both humans and animals, sometimes even following a single conditioning trial, and is usually maintained for long periods [63]. Importantly, and similarly to the physiological responses found in insomnia, fearful stimuli (both innately aversive and conditioned) also increase sympathetic nerve activity and induce a state of hyperarousal (CR), as reflected by increased heart rate, cortisol levels, alertness, emotional reactivity, cognitive processing, electrodermal activity and fast EEG frequencies (in the beta/gamma band) [64–66]. On the other hand, fear extinction is defined as the gradual decrease of the CR, because the CS no longer predicts the US [25,26]. During fear extinction, an inhibitory (CS-noUS) memory that opposes the expression of the original fear (CS-US) memory is formed [67], due to molecular changes within the basolateral amygdala. The new extinction memory later undergoes consolidation, by way of the basolateral amygdala, ventromedial prefrontal cortex (vmPFC), and the hippocampus. The retrieval of the extinction memory is related to increased activity in the vmPFC, which exerts an inhibitory control on fear expression by decreasing amygdala output [62]. Fear extinction is reflected by decreased arousal, such as decreased electrodermal activity, anterior theta and amygdala responses [68] and increased gamma oscillations in the (inhibitory) vmPFC [69].

The persistence of fear in the absence of any imminent threat is a hallmark of anxiety disorders [70]. Impaired ability to acquire or retrieve extinction learning may underlie such pathological anxiety [26]. Importantly, a delay of fear extinction is also found in chronic insomnia without comorbidity [71].

Delayed fear extinction and cortical hyperarousal in insomnia disorder

During fear conditioning, patients with insomnia disorder demonstrated activity in the ACC and the anterior insula, regions which are typically related to the expression of conditioned fear [71]. Moreover, poorer sleep quality was associated with greater activation of these regions. This study supports the idea that, compared to controls, insomnia patients may demonstrate enhanced anticipation of aversive threat-related events [71]. During the phase of extinction learning, when controls activated the vmPFC, the patients showed no significant activity in this region. During early extinction recall, the patients showed activation in regions related to both fear expression (amygdala, insula, ACC) and fear extinction (vmPFC), pointing out the presence of delayed fear extinction in chronic insomnia [71].

A similar conclusion, of delayed resolution of emotional distress, comes from a study showing that chronic insomnia patients have reduced overnight resolution of emotional distress due to restless REM sleep [72]. Recently, the same research group showed that, compared to good sleepers, patients with insomnia disorder have a stronger recruitment of the limbic circuit, in particular the dorsal ACC (dACC), and stronger galvanic skin responses when remembering long-term emotional memories [73]. Such difference between the groups was not found for novel emotional memories. Based on this finding the authors conclude that insomnia disorder involves a deficiency to dissociate the limbic circuit (especially the dACC) from the emotional memory trace.

Additional work comparing chronic insomnia patients to healthy controls also demonstrated a decreased functional connectivity between the amygdala, insula, striatum and thalamus, and, at the same time, an increased functional connectivity between the amygdala, premotor cortex and sensorimotor cortex [74]. As the amygdala is the main region implicated in fear conditioning processes, these results seem to further support dysfunctional fear processes and elevated motor readiness for 'fight-or-flight' responses in insomnia disorder.

Therefore, some individuals with chronic insomnia demonstrate stronger fear conditioning than controls and a delay or failure in extinction learning. In some of these patients, even in the absence of any stressors, some CS (e.g., bed, bedtime, place, thoughts or mental images) produce wakefulness. This concept seems to be in accordance with the so-called 'hyperarousal model' of chronic insomnia [13]. Hyperarousal in chronic insomnia is both somatic (physiological) and cortical. Similar to acute insomnia, physiological arousal in chronic insomnia is reflected by increased electrodermal activity [75], heart rate [76] and cortisol levels [77] compared to controls. Cortical hyperarousal refers to enhanced information processing and cognitive activities at bedtime, as reflected by higher beta and gamma power at bedtime or during sleep of people with chronic insomnia [13,19,52,53,78]. Neuroimaging studies show that chronic insomnia is characterized by persistent wake-like activity in neural structures during sleep, resulting in simultaneous waking and sleeping neural activity patterns [79,80]. These local activations [81–83] may explain why these individuals continue being awake or aware of the external environment despite the occurrence of a more global EEG sleep pattern.

According to the current model, when the initial stressor (US) that caused acute insomnia is absent, and if fear conditioning (CS→CR) has taken place during a 'sensitive' period (during probably the so-called transient or subchronic insomnia, see also section Cognitive behavioral therapy (CBT)), specific CS (e.g., bed, place, etc) can maintain the CR (conditioned wakefulness/arousal) for long periods and explain chronic insomnia. These stimuli should normally be compatible with sleep, but they become incompatible due to their association with the US. The unconditioned response-UR (wakefulness in acute insomnia) and the CR (wakefulness in chronic insomnia) are both reflected by a physiological and cortical hyperarousal (i.e., a similar response as found in all states of conditioned fear, see also section Fear conditioning and fear extinction). This hyperarousal would be an adaptive physiological response to stress in acute insomnia -especially in the instance of real danger- and a maladaptive response to non-extinguished conditioned stimuli in chronic insomnia. Therefore, we suggest that one primary focus of

treatment for chronic insomnia should address this dysfunctional fear extinction (see section An evolutionary medicine approach to the treatment of chronic insomnia).

An evolutionary medicine approach to the treatment of chronic insomnia

Taking an evolutionary perspective on insomnia can enhance our understanding of the etiology of this disorder and in many cases provide new treatment options [84,85]. Under such a perspective, clinicians should seek alternative treatments in order to alleviate the sources of anxiety and stress characterizing chronic insomnia [86]. According to this model, an efficient therapy for chronic insomnia should attempt to identify the CS and the US, and to enhance extinction learning in order to decrease the hyperarousal/wakefulness (CR) over time. This is interpreted as learning new, inhibitory CS-noUS associations (extinction or safety memory), which oppose the original CS-US associations (threat memory) [26]. Therefore, accelerating fear extinction and the return to safety would be the main objectives of such personalized and emotion-based treatment for chronic insomnia. These treatments would include pharmacotherapy and cognitive-behavioral therapy.

Pharmacotherapy

Some medications have been used in the past in order to extinguish a CS. D-cycloserine, an N-methyl-D-aspartate glutamate receptor partial agonist, facilitates extinction learning and enhances extinction-related brain activation [87]. Valpoic acid, a histone deacetylase inhibitor, also enhances fear extinction and prevents new acquisition of fear conditioning [88], both in wakefulness and sleep [89]. Studies testing for the efficacy of valpoic acid and D-cycloserine in chronic insomnia are needed. Prazosin, a a1-adrenergic receptor antagonist, and beta-blockers (e.g., propranolol), have also been found to enhance fear extinction processes in rats [90] and humans [91] respectively. Cannabinoid receptor type 1 (CB1) receptor agonists accelerate extinction learning [92], and are known to improve sleep continuity and to reduce sleep latency [93]. Finally, a recent animal study showed that melatonin facilitates the extinction of conditional cued fear [94]. Melatonin seems to increase REM duration [95] and its chronic use may successfully treat chronic insomnia [96], although its modest effects [97] indicate the existence of different insomnia phenotypes. Both the sopoforic effects of CB1 agonists and melatonin and their effects on fear extinction (including sleep-dependent ones) could be used as an efficient treatment of chronic insomnia.

Cognitive behavioral therapy (CBT)

Under the scope of the current emotional model of insomnia, a personalized emotion-related CBT should be in the center of the management of chronic insomnia, as fear extinction has been considered the main psychophysiological mechanism behind this therapy [98]. Exposure therapy may be particularly suited for enhancing extinction (inhibitory) learning [26], allowing the patient to emotionally engage and process the stressful memories in the absence of the feared outcomes. This ultimately leads to the creation of a non-fearful (safety or extinction) memory. Several methods can be used in order to enhance extinction learning of exposure therapy (e.g., positive affect induction, violation of expectancy, context attenuation, mental rehearsal of CS-noUS associations) [26], once the CS and US are sufficiently identified. Interestingly, extinguishing wake-promoting CS reminds us of the quasi-desensitization treatment [99,100], where repeated pairing of neutral cues (e.g., visual imagery of neutral activities) with some CS (e.g., clock watching) may also reduce insomnia symptoms and conditioned arousal. Repeated pairing of sleep-related cues with sleep (e.g., rocking bed or other external stimuli) [101–103] may also enhance the extinction process. In addition, cognitive strategies should address other conscious thoughts associated with negative affect and which reinforce conditioned arousal, such as anxious anticipation of sleeplessness.

The use of medication (e.g., valproid acid, melatonin) and of psychotherapeutic techniques that enhance extinction could be done during both the chronic phase of insomnia, which is characterized by delayed/failed extinction and the period of transient (2–4 wks of symptoms) and subchronic insomnia (symptoms >1 mo but <3 ms). During this period, classical (fear) conditioning processes may occur [24], therefore it represents a critical window during which fear extinction may be better manipulated and enhanced. This would ultimately prevent the transition from acute to chronic insomnia. More phenomenological studies identifying specific insomnia phenotypes are needed in order to develop such personalized therapies (see also section Strengths and limitations of the model). Importantly, a single CS may not be responsible for the maintenance of chronic insomnia. Both cued and contextual fear conditioning components have to be addressed for an efficient emotion-based cognitive-behavioral treatment of insomnia. The systematic measurement of indices of sympathetic activity and of fear conditioning/extinction (e.g., electrodermal activity, heart rate, cortisol levels, theta/gamma oscillations) before, during and after treatment may provide supplementary support for the current hypothesis and assess treatment efficiency across several time-points.

Strengths and limitations of the model

The current model may complement other models of insomnia. Notably, it takes into account the evolutionary origin of this disorder, the role of emotional processing in its pathophysiology, and it attempts to explain the transition from acute to chronic insomnia.

Other models of insomnia have described this transition. The traditional Three-Factor (3P) behavioral model [18] considers how behaviors and cognitions adopted by the individual to cope with acute insomnia would actually reinforce the problem and produce chronic insomnia, by instrumental conditioning. However, it has been suggested that if only instrumental factors would account for chronic insomnia, CBT for insomnia (CBT-I) would produce more than 50% of remission in the acute treatment phase [24]. Importantly, previous to the current proposed model, the 4P model [24], an extension of the 3P model, and the neurocognitive model [19] had already taken into account classical conditioning as a perpetuating factor of insomnia. On the other hand, the cognitive model [104] proposes that the transition from acute to chronic insomnia occurs when sleep-related worry makes patients selectively attend to sleep-related threats and the daytime consequences of insomnia. Nevertheless, no model we know of considers the emotional component of the disorder or the role of fear extinction in the pathophysiology of transition between acute and chronic insomnia. This emotional (fear) perspective, which is based on recent empirical evidence from neuroimaging, clinical, anthropological and sociological studies, differentiates it from other evolutionary

approaches [11]. For example, environmental safety and other environmental factors (e.g., food insecurity, 'sentinalized' sleep patterns) have been largely neglected from insomnia models, with only few of them claiming that acute insomnia may be vestigial [7,11]. Finally, the current models do not address sufficiently whether acute and chronic insomnia are distinct entities or if the same hyperarousal mechanism accounts for both of them and for the three forms of insomnia (initial, middle, late). Our evolutionary-emotional model of insomnia – with its emphasis on the delay of fear extinction – addresses some of these missing points opening the way to more studies, which should thoroughly explore the origins (e.g., threats vs food insecurity) and differences of initial, middle and late insomnia, one of the least addressed issues in the insomnia literature.

Another strength of the model is that it supports the existence of strong links between insomnia and anxiety, as fear conditioning is central in the pathophysiology of anxiety disorders [105]. Unlike other sleep disorders, such as sleep apneas, an associated stress is a strong determinant for the pathophysiology of acute insomnia, with an external or internal stressor usually triggering episodes of insomnia. Stress may involve both negative and positive events. For example, overall cortisol levels on the two ds before a positive event (e.g., a holiday) were above normal in children reporting positive expectations for this event [106]. Emotional/reward systems respond to opportunities when they come with significant uncertainty, i.e., prediction error [107]. With respect to acute insomnia, one could potentially broaden the current view from threats to unexpected opportunities, independently of their emotional valence.

Yet, fear conditioning is not and cannot be the only pathophysiological mechanism of chronic insomnia, nor can a dysregulated extinction learning account exclusively for the transition to chronicity. In the previous version of ICSD [108], insomnia was subdivided into several subtypes (e.g., psychophysiological, paradoxical, idiopathic, inadequate sleep hygiene, insomnia due to drug or substance, insomnia due to a medical condition). Our model can sufficiently explain psychophysiological insomnia and insomnia associated with a psychiatric disease (like an anxiety or trauma-related disorder); these are very common forms of chronic insomnia, clearly associated with hyperarousal and fear conditioning. On the other hand, paradoxical insomnia is possibly the most obscure and less understood variant of insomnia [109], along with idiopathic insomnia [110], and it can't be excluded that other unknown factors play a significant role in the pathophysiology of these subtypes. However, it should be noted that insomnia subtypes have been currently removed from current classifications [5,12] after the observation that inter-rater agreement was very poor [111]. Indeed, their boundaries and definitions are extremely blurred, possibly due to the fact that paths inducing insomnia are often multifactorial and different subtypes may partially overlap in the same subject. For example, insomnia symptoms due to organic conditions (e.g., physical disease, injuries, pain, starvation, etc) are known to be sustained by different neurobiological systems from those due to real or perceived threats, although sometimes two pathways may coexist (e.g., for physical conditions implying both pain and a threat for survival).

Moreover, patients with insomnia disorder are characterized by high heterogeneity in terms of mood, personality traits, life events, coping strategies and cognition [112]. Five insomnia disorder subtypes have been recently described according to the degree of distress, reward sensitivity and reactivity to life events of patients [113]. Subtype 1 is characterized by high general distress, subtype 2 with moderate distress/high reward sensitivity, subtype 3 with moderate distress/low reward sensitivity, subtype 4 with low distress/high reactivity and subtype 5 with low distress/low reactivity. It has been proposed that these phenotypes underlie distinct causes of chronic insomnia and respond differently to treatment [113]. It is likely that the current model can better explain the subtype 4, characterized by longer duration of insomnia response to life events, high emotional reactivity and more frequent childhood trauma [113]. Patients with this subtype experience standard tones as more salient and emotionally relevant than controls (as shown by ERPs) [113], supporting a delay in extinction and a deficiency to downregulate emotional distress over time. As subtypes 1 and 2 are characterized by high pre-sleep arousal, one could include them in the model too. Future work should investigate insomnia phenotypes in relation to the extinction of the fear response in order to better identify underlying insomnia mechanisms and develop personalized therapies.

Testing the hypotheses and predictions of the current perspective will require 1) natural history and observational studies in both small-scale societies [32,33,114] and economically developed or developing countries (in both safe and less safe neighborhoods), 2) longitudinal studies attempting to determine the specific role of genetics, neurobiology, personality traits and stressful environmental events in the etiology of acute/chronic insomnia, 3) studies using experimentally induced stress in the laboratory [115,116], and 4) treatment trials, in order to test if targeting specific threat memories alleviate the symptoms of chronic insomnia.

Conclusions

In this comprehensive hypothesis-driven review, we maintain that insomnia can be the result of an evolutionary survival mechanism. The current perspective considers that insomnia may have evolutionary origins and takes into account the role of emotional processing and individual factors in its pathophysiology. Moreover, it attempts to explain the transient form of insomnias, which is related (but not always) to an adaptive stress response to a perceived or real threat, and a more persistent (pathological) form of this disorder, where a failure or delay of extinction learning accounts at least partly for its pathophysiology. Finally, it proposes potential specific treatments, such as cognitive-behavioral therapy focused on specific threat memories. Future longitudinal and natural history studies of insomnia disorder would shed more light on the understanding of the pathophysiology of this disorder.

Practice points

In this paper it is proposed that:

1) Acute insomnia reflects an evolutionary survival mechanism and an adaptive response to real or perceived stress;
2) Such a mechanism seems dysfunctional in modern society due to radical improvements in environmental safety;
3) Failure to extinguish the real or perceived threat would account, at least partly, for their persistence over time and the chronic form of insomnia in some individuals;
4) Accelerating fear extinction and the return to safety by pharmacotherapy and cognitive-behavioral therapy, would be the main objectives of a personalized and emotion-based treatment for insomnia.

Research agenda

Testing the hypotheses and predictions of this model will require:

1) Natural history studies in both small-scale and economically developed societies;
2) Longitudinal studies searching for the specific role of genetics, personality traits, neurophysiology and stress in the etiology of acute/chronic insomnia;
3) More studies using experimentally induced stress in the laboratory;
4) Clinical trials, in order to test if treatments targeting fear extinction improve symptoms of insomnia disorder.

Conflicts of interest

The authors do not have any conflicts of interest to disclose.

Acknowledgments

The authors would like to thank C. Robert Cloninger, Marco Del Giudice, Eva Pool, Sophie Schwartz and Stephen Perrig for the helpful discussions about this paper. LP is funded by the Geneva University Hospitals (PRD 18-2019-I) and the Swiss National Science Foundation (CRSK-3_190722). TDV is funded by the Natural Sciences and Engineering Research Council of Canada (RGPIN 436006-2013), the Canadian Institutes of Health Research (MOP 142191, PJT 153115 and PJT 156125), the Fonds de Recherche du Québec (Santé) (251602) and the Canada Foundation for Innovation (33716).

References

[1] Buysse DJ. Insomnia. JAMA 2013;309(7):706–16.
[2] Stein MB, McCarthy MJ, Chen CY, Jain S, Gelernter J, He F, et al. Genome-wide analysis of insomnia disorder. Mol Psychiatr 2018;23(11):2238–50.
[3] Park JH, An H, Jang ES, Chung S. The influence of personality and dysfunctional sleep-related cognitions on the severity of insomnia. Psychiatr Res 2012;197(3):275–9.
[4] Zwir I, Arnedo J, Del-Val C, Pulkki-Raback L, Konte B, Yang SS, et al. Uncovering the complex genetics of human character. Mol Psychiatr 2018. https://doi.org/10.1038/s41380-018-0263-6.
[5] American Academy of Sleep Medicine. ICSD-3—international classification of sleep disorders. In: Diagnostic and coding manual. Illinois. 3nd ed. Darien: American Academy of Sleep Medicine; 2014. p. 19–46.
[6] Perlis ML, Vargas I, Ellis JG, Grandner MA, Morales KH, Gencarelli A, et al. The natural history of insomnia: the incidence of acute insomnia and subsequent progression to chronic insomnia or recovery in good sleeper subjects. Sleep; 2019. https://doi.org/10.1093/sleep/zsz299. pii: zsz299.
*[7] Ellis JG, Gehrman P, Espie CA, Riemann D, Perlis ML. Acute insomnia: current conceptualizations and future directions. Sleep Med Rev 2012;16(1):5–14.
[8] Spielman A, Glovinsky P. The varied nature of insomnia. New York: Plenum Press; 1991. PH.
[9] McNamara P, Auerbach S. Evolutionary medicine of sleep disorders: toward a science of sleep duration. New York, NY: Cambridge University Press; 2010.
[10] Riemann D, Spiegelhalder K, Feige B, Voderholzer U, Berger M, Perlis M, et al. The hyperarousal model of insomnia: a review of the concept and its evidence. Sleep Med Rev 2010;14(1):19–31.
*[11] Nunn CL, Samson DR, Krystal AD. Shining evolutionary light on human sleep and sleep disorders. Evol Med Public Health 2016;2016(1):227–43.
[12] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington, VA: American Psychiatric Publishing; 2013.
*[13] Bonnet MH, Arand DL. Hyperarousal and insomnia: state of the science. Sleep Med Rev 2010;14(1):9–15.
[14] Morin CM, Belanger L, LeBlanc M, Ivers H, Savard J, Espie CA, et al. The natural history of insomnia: a population-based 3-year longitudinal study. Arch Intern Med 2009;169(5):447–53.
[15] LeBlanc M, Merette C, Savard J, Ivers H, Baillargeon L, Morin CM. Incidence and risk factors of insomnia in a population-based sample. Sleep 2009;32(8):1027–37.
[16] Buysse DJ, Angst J, Gamma A, Ajdacic V, Eich D, Rossler W. Prevalence, course, and comorbidity of insomnia and depression in young adults. Sleep 2008;31(4):473–80.
[17] Jansson-Frojmark M, Linton SJ. The course of insomnia over one year: a longitudinal study in the general population in Sweden. Sleep 2008;31(6):881–6.
[18] Spielman AJ, Caruso LS, Glovinsky PB. A behavioral perspective on insomnia treatment. Psychiatr Clin North Am 1987;10(4):541–53.
[19] Perlis ML, Giles DE, Mendelson WB, Bootzin RR, Wyatt JK. Psychophysiological insomnia: the behavioural model and a neurocognitive perspective. J Sleep Res 1997;6(3):179–88.
[20] Pigeon WR. Treatment of adult insomnia with cognitive-behavioral therapy. J Clin Psychol 2010;66(11):1148–60.
[21] Olsson A, Phelps EA. Social learning of fear. Nat Neurosci 2007;10(9):1095–102.
[22] Shechner T, Hong M, Britton JC, Pine DS, Fox NA. Fear conditioning and extinction across development: evidence from human studies and animal models. Biol Psychol 2014;100:1–12.
[23] LeDoux JE. Coming to terms with fear. Proc Natl Acad Sci U S A 2014;111(8):2871–8.
[24] Perlis M, Ellis JG, Kloss JD, Riemann D. In: Kryger M, Roth T, Dement W, editors. Etiology and pathophysiology of insomnia. New York: Elsevier; 2016.
[25] Myers KM, Davis M. Mechanisms of fear extinction. Mol Psychiatr 2007;12(2):120–50.
*[26] Craske MG, Hermans D, Vervliet B. State-of-the-art and future directions for extinction as a translational model for fear and anxiety. Philos T R Soc B 2018 2018;373(1760):20170025.
[27] Maddox SA, Hartmann J, Ross RA, Ressler KJ. Deconstructing the gestalt: mechanisms of fear, threat, and trauma memory encoding. Neuron 2019;102(1):60–74.
[28] Diaz-Mataix L, Piper WT, Schiff HC, Roberts CH, Campese VD, Sears RM, et al. Characterization of the amplificatory effect of norepinephrine in the acquisition of Pavlovian threat associations. Learn Mem 2017;24(9):432–9.
[29] Li NP, van Vugt M, Colarelli SM. The evolutionary mismatch hypothesis: implications for psychological science. Curr Dir Psychol Sci 2018;27(1):38–44.
[30] Power ML. The human obesity epidemic, the mismatch paradigm, and our modern "captive" environment. Am J Hum Biol 2012;24(2):116–22.
[31] Lesku JA, Roth TC, Rattenborg NC, Amlaner CJ, Lima SL. Phylogenetics and the correlates of mammalian sleep: a reappraisal. Sleep Med Rev 2008;12(3):229–44.
[32] Yetish G, Kaplan H, Gurven M, Wood B, Pontzer H, Manger PR, et al. Natural sleep and its seasonal variations in three pre-industrial societies. Curr Biol 2015;25(21):2862–8.
*[33] Samson DR, Crittenden AN, Mabulla IA, Mabulla AZP, Nunn CL. Chronotype variation drives night-time sentinel-like behaviour in hunter-gatherers. Proc Biol Sci 2017;284(1858).
[34] Samson DR, Crittenden AN, Mabulla AI, Mabulla AZP, Nunn CL. Hadza sleep biology: evidence for flexible sleep-wake patterns in hunter-gatherers. Am J Phys Anthropol 2017;162(3):573–82.
[35] Hill TD, Trinh HN, Wen M, Hale L. Perceived neighborhood safety and sleep quality: a global analysis of six countries. Sleep Med 2016;18:56–60.
[36] Lavie P, Carmeli A, Mevorach L, Liberman N. Sleeping under the threat of the Scud: war-related environmental insomnia. Isr J Med Sci 1991;27(11–12):681–6.
[37] Grandner MA, Petrov ME, Rattanaumpawan P, Jackson N, Platt A, Patel NP. Sleep symptoms, race/ethnicity, and socioeconomic position. J Clin Sleep Med 2013;9(9):897–905. A-D.
[38] Troxel WM, Haas A, Ghosh-Dastidar B, Richardson AS, Hale L, Buysse DJ, et al. Food insecurity is associated with objectively measured sleep problems. Behav Sleep Med 2019. https://doi.org/10.1080/15402002.2019.1669605.
[39] Patel NP, Grandner MA, Xie DW, Branas CC, Gooneratne N. "Sleep disparity" in the population: poor sleep quality is strongly associated with poverty and ethnicity. BMC Publ Health 2010 Aug 11;10:475. https://doi.org/10.1186/1471-2458-10-475.
[40] Silberbauer G. Hunter and habitat in the central kalahari desert. Cambridge, England: Cambridge University Press; 1981. p. 111.
[41] Samson DR, Manus MB, Krystal AD, Fakir E, Yu JJ, Nunn CL. Segmented sleep in a nonelectric, small-scale agricultural society in Madagascar. Am J Hum Biol 2017:1–13.
[42] Samson DR, Crittenden AN, Mabulla IA, Mabulla AZP, Nunn CL. Does the moon influence sleep in small-scale societies. Sleep Health 2018.
[43] Ekirch AR. At day's close: night in times past. WW Norton & Company; 2006.

* The most important references are denoted by an asterisk

[44] Worthman CM, editor. After dark: the evolutionary ecology of human sleep. Oxford: Oxford University Press; 2008.
[45] Cano G, Mochizuki T, Saper CB. Neural circuitry of stress-induced insomnia in rats. J Neurosci 2008;28(40):10167–84.
[46] Tamaki M, Nittono H, Hayashi M, Hori T. Spectral analysis of the first-night effect on the sleep-onset period. Sleep Biol Rhythm 2005;3(3):122–9.
*[47] Tamaki M, Bang JW, Watanabe T, Sasaki Y. Night watch in one brain hemisphere during sleep associated with the first-night effect in humans. Curr Biol 2016;26(9):1190–4.
[48] Scholle S, Scholle HC, Kemper A, Glaser S, Rieger B, Kemper G, et al. First night effect in children and adolescents undergoing polysomnography for sleep-disordered breathing. Clin Neurophysiol 2003;114(11):2138–45.
[49] Lester BK, Burch NR, Dossett RC. Nocturnal EEG-GSR profiles: the influence of presleep states. Psychophysiology 1967;3(3):238–48.
[50] Jung C, Greco S, Nguyen HH, Ho JT, Lewis JG, Torpy DJ, et al. Plasma, salivary and urinary cortisol levels following physiological and stress doses of hydrocortisone in normal volunteers. BMC Endocr Disord 2014;14:91.
[51] Khoo B, Boshier PR, Freethy A, Tharakan G, Saeed S, Hill N, et al. Redefining the stress cortisol response to surgery. Clin Endocrinol 2017;87(5):451–8.
[52] Freedman RR. EEG power spectra in sleep-onset insomnia. Electroencephalogr Clin Neurophysiol 1986;63(5):408–13.
[53] Perlis ML, Smith MT, Andrews PJ, Orff H, Giles DE. Beta/Gamma EEG activity in patients with primary and secondary insomnia and good sleeper controls. Sleep 2001;24(1):110–7.
[54] Saper CB, Cano G, Scammell TE. Homeostatic, circadian, and emotional regulation of sleep. J Comp Neurol 2005;493(1):92–8.
[55] Saper CB, Fuller PM, Pedersen NP, Lu J, Scammell TE. Sleep state switching. Neuron 2010;68(6):1023–42.
[56] Chou TC, Bjorkum AA, Gaus SE, Lu J, Scammell TE, Saper CB. Afferents to the ventrolateral preoptic nucleus. J Neurosci 2002;22(3):977–90.
[57] Sutton DA, Moldofsky H, Badley EM. Insomnia and health problems in Canadians. Sleep 2001;24(6):665–70.
[58] Hossain JL, Shapiro CM. The prevalence, cost implications, and management of sleep disorders: an overview. Sleep Breath 2002;6(2):85–102.
[59] Groeger JA, Zijlstra FRH, Dijk DJ. Sleep quantity, sleep difficulties and their perceived consequences in a representative sample of some 2000 British adults. J Sleep Res 2004;13(4):359–71.
[60] Stranges S, Tigbe W, Gomez-Olive FX, Thorogood M, Kandala NB. Sleep problems: an emerging global epidemic? Findings from the IN DEPTH WHO-SAGE study among more than 40,000 older adults from 8 countries across Africa and Asia. Sleep 2012;35(8):1173–81.
[61] Petit D, Touchette E, Tremblay RE, Boivin M, Montplaisir J. Dyssomnias and parasomnias in early childhood. Pediatrics 2007;119(5):e1016–25.
[62] Quirk GJ, Mueller D. Neural mechanisms of extinction learning and retrieval. Neuropsychopharmacology 2008;33(1):56–72.
[63] Maren S. Neurobiology of Pavlovian fear conditioning. Annu Rev Neurosci 2001;24:897–931.
[64] Zheng J, Anderson KL, Leal SL, Shestyuk A, Gulsen G, Mnatsakanyan L, et al. Amygdala-hippocampal dynamics during salient information processing. Nat Commun 2017;8:14413.
[65] Putman P, van Peer J, Maimari I, van der Werff S. EEG theta/beta ratio in relation to fear-modulated response-inhibition, attentional control, and affective traits. Biol Psychol 2010;83(2):73–8.
[66] Adolphs R. The biology of fear. Curr Biol 2013;23(2):R79–93.
[67] Milad MR, Quirk GJ. Fear extinction as a model for translational neuroscience: ten years of progress. Annu Rev Psychol 2012;63:129–51.
[68] Sperl MFJ, Panitz C, Rosso IM, Dillon DG, Kumar P, Hermann A, et al. Fear extinction recall modulates human frontomedial theta and amygdala activity. Cerebr Cortex 2019;29(2):701–15.
[69] Mueller EM, Panitz C, Hermann C, Pizzagalli DA. Prefrontal oscillations during recall of conditioned and extinguished fear in humans. J Neurosci 2014;34(21):7059–66.
[70] Graham BM, Milad MR. The study of fear extinction: implications for anxiety disorders. Am J Psychiatr 2011;168(12):1255–65.
*[71] Seo J, Moore KN, Gazecki S, Bottary RM, Milad MR, Song H, et al. Delayed fear extinction in individuals with insomnia disorder. Sleep 2018;41(8).
[72] Wassing R, Benjamins JS, Dekker K, Moens S, Spiegelhalder K, Feige B, et al. Slow dissolving of emotional distress contributes to hyperarousal. Proc Natl Acad Sci U S A 2016;113(9):2538–43.
*[73] Wassing R, Schalkwijk F, Lakbila-Kamal O, Ramautar JR, Stoffers D, Mutsaerts H, et al. Haunted by the past: old emotions remain salient in insomnia disorder. Brain 2019;142(6):1783–96.
*[74] Huang Z, Liang P, Jia X, Zhan S, Li N, Ding Y, et al. Abnormal amygdala connectivity in patients with primary insomnia: evidence from resting state fMRI. Eur J Radiol 2012;81(6):1288–95.
[75] Broman JE, Hetta J. Electrodermal activity in patients with persistent insomnia. J Sleep Res 1994;3(3):165–70.
[76] Bonnet MH, Arand DL. Heart rate variability in insomniacs and matched normal sleepers. Psychosom Med 1998;60(5):610–5.
[77] Vgontzas AN, Bixler EO, Lin HM, Prolo P, Mastorakos G, Vela-Bueno A, et al. Chronic insomnia is associated with nyctohemeral activation of the hypothalamic-pituitary-adrenal axis: clinical implications. J Clin Endocrinol Metab 2001;86(8):3787–94.
[78] Colombo MA, Ramautar JR, Wei Y, Gomez-Herrero G, Stoffers D, Wassing R, et al. Wake high-density electroencephalographic spatiospectral signatures of insomnia. Sleep 2016;39(5):1015–27.
[79] Buysse DJ, Germain A, Hall M, Monk TH, Nofzinger EA. A neurobiological model of insomnia. Drug Discov Today Dis Model 2011;8(4):129–37.
[80] Nofzinger EA, Buysse DJ, Germain A, Price JC, Miewald JM, Kupfer DJ. Functional neuroimaging evidence for hyperarousal in insomnia. Am J Psychiatr 2004;161(11):2126–8.
[81] Nobili L, Ferrara M, Moroni F, De Gennaro L, Russo GL, Campus C, et al. Dissociated wake-like and sleep-like electro-cortical activity during sleep. Neuroimage 2011;58(2):612–9.
[82] Engelhard Christensen J, Wassing R, Wei Y, Van Someren EJ. Data-driven analysis of EEG reveals concomitant superficial sleep during deep sleep in insomnia disorder. Front Neurosci 2019;13:598.
[83] Feige B, Al-Shajlawi A, Nissen C, Voderholzer U, Hornyak M, Kloepfer C, et al. Does REM sleep contribute to subjective wake time in primary insomnia? A comparison of polysomnographic and subjective sleep in 100 patients and matched controls. J Sleep Res 2008;17:196.
[84] Stearns SC, editor. Evolution in health and disease. New York: Oxford; 1999.
[85] Perlman R. Evolution and medicine. Oxford: Oxford University Press; 2013.
[86] McNamara P, Auerbach S. Evolutionary medicine of sleep disorders: toward a science of sleep duration. In: McNamara P, Barton RA, Nunn CL, editors. Evolution of sleep. Cambridge, UK: Cambridge University Press; 2010. p. 107–22.
[87] Klass A, Glaubitz B, Tegenthoff M, Lissek S. d-Cycloserine facilitates extinction learning and enhances extinction-related brain activation. Neurobiol Learn Mem 2017;144:235–47.
[88] Kuriyama K, Honma M, Soshi T, Fujii T, Kim Y. Effect of D-cycloserine and valproic acid on the extinction of reinstated fear-conditioned responses and habituation of fear conditioning in healthy humans: a randomized controlled trial. Psychopharmacology (Berl) 2011;218(3):589–97.
[89] Kuriyama K, Honma M, Yoshiike T, Kim Y. Valproic acid but not D-cycloserine facilitates sleep-dependent offline learning of extinction and habituation of conditioned fear in humans. Neuropharmacology 2013;64:424–31.
[90] Lucas EK, Wu WC, Roman-Ortiz C, Clem RL. Prazosin during fear conditioning facilitates subsequent extinction in male C57Bl/6N mice. Psychopharmacology (Berl) 2018.
[91] Giustino TF, Fitzgerald PJ, Maren S. Revisiting propranolol and PTSD: memory erasure or extinction enhancement? Neurobiol Learn Mem 2016;130:26–33.
[92] Rabinak CA, Angstadt M, Sripada CS, Abelson JL, Liberzon I, Milad MR, et al. Cannabinoid facilitation of fear extinction memory recall in humans. Neuropharmacology 2013;64(1):396–402.
[93] Pava MJ, Makriyannis A, Lovinger DM. Endocannabinoid signaling regulates sleep stability. PloS One 2016;11(3). e0152473.
[94] Huang F, Yang Z, Liu X, Li CQ. Melatonin facilitates extinction, but not acquisition or expression, of conditional cued fear in rats. BMC Neurosci 2014;15:86.
[95] Kunz D, Mahlberg R, Muller C, Tilmann A, Bes F. Melatonin in patients with reduced REM sleep duration: two randomized controlled trials. J Clin Endocrinol Metab 2004;89(1):128–34.
[96] Zwart TC, Smits MG, Egberts TCG, Rademaker CMA, van Geijlswijk IM. Long-term melatonin therapy for adolescents and young adults with chronic sleep onset insomnia and late melatonin onset: evaluation of sleep quality, chronotype, and lifestyle factors compared to age-related randomly selected population cohorts. Healthcare (Basel). 2018;6(1).
[97] Ferracioli-Oda E, Qawasmi A, Bloch MH. Meta-analysis: melatonin for the treatment of primary sleep disorders. PloS One 2013;8(5). e63773.
[98] Craske MG, Kircanski K, Zelikowsky M, Mystkowski J, Chowdhury N, Baker A. Optimizing inhibitory learning during exposure therapy. Behav Res Ther 2008;46(1):5–27.
[99] Steinmark SW, Borkovec TD. Active and placebo treatment effects on moderate insomnia under counterdemand and positive demand instructions. J Abnorm Psychol 1974;83(2):157–63.
[100] Edinger JD, Wohlgemuth WK, Radtke RA, Marsh GR, Quillian RE. Cognitive behavioral therapy for treatment of chronic primary insomnia: a randomized controlled trial. J Am Med Assoc 2001;285(14):1856–64.
[101] Perrault AA, Khani A, Quairiaux C, Kompotis K, Franken P, Muhlethaler M, et al. Whole-night continuous rocking entrains spontaneous neural oscillations with benefits for sleep and memory. Curr Biol 2019;29(3):402–11. e3.
[102] Perl O, Arzi A, Sela L, Secundo L, Holtzman Y, Samnon P, et al. Odors enhance slow-wave activity in non-rapid eye movement sleep. J Neurophysiol 2016;115(5):2294–302.
[103] Bellesi M, Riedner BA, Garcia-Molina GN, Cirelli C, Tononi G. Enhancement of sleep slow waves: underlying mechanisms and practical consequences. Front Syst Neurosci 2014;8:208.
[104] Harvey AG. A cognitive model of insomnia. Behav Res Ther 2002;40(8):869–93.
[105] Shin LM, Liberzon I. The neurocircuitry of fear, stress, and anxiety disorders. Neuropsychopharmacology 2010;35(1):169–91.

[106] Flinn MV, Nepomnaschy PA, Muehlenbein MP, Ponzi D. Evolutionary functions of early social modulation of hypothalamic-pituitary-adrenal axis development in humans. Neurosci Biobehav Rev 2011;35(7):1611–29.
[107] Schultz W, Dickinson A. Neuronal coding of prediction errors. Annu Rev Neurosci 2000;23:473–500.
[108] American Academy of Sleep Medicine. ICSD-2—international classification of sleep disorders. In: Diagnostic and coding manual. Illinois. 2nd ed. Darien: American Academy of Sleep Medicine; 2005.
[109] Castelnovo A, Ferri R, Punjabi NM, Castronovo V, Garbazza C, Zucconi M, et al. The paradox of paradoxical insomnia: a theoretical review towards a unifying evidence-based definition. Sleep Med Rev 2019;44:70–82.
[110] Espie CA, Barrie LM, Forgan GS. Comparative investigation of the psychophysiologic and idiopathic insomnia disorder phenotypes: psychologic characteristics, patients' perspectives, and implications for clinical management. Sleep 2012;35(3):385–93.
[111] Edinger JD, Wyatt JK, Stepanski EJ, Olsen MK, Stechuchak KM, Carney CE, et al. Testing the reliability and validity of DSM-IV-TR and ICSD-2 insomnia diagnoses. Results of a multitrait-multimethod analysis. Arch Gen Psychiatr 2011;68(10):992–1002.
[112] Benjamins JS, Migliorati F, Dekker K, Wassing R, Moens S, Blanken TF, et al. Insomnia heterogeneity: characteristics to consider for data-driven multivariate subtyping. Sleep Med Rev 2017;36:71–81.
*[113] Blanken TF, Benjamins JS, Borsboom D, Vermunt JK, Paquola C, Ramautar J, et al. Insomnia disorder subtypes derived from life history and traits of affect and personality. Lancet Psychiatry 2019;6(2):151–63.
[114] Knutson KL. Sleep duration, quality, and timing and their associations with age in a community without electricity in Haiti. Am J Hum Biol 2014;26(1):80–6.
[115] Kim EJ, Dimsdale JE. The effect of psychosocial stress on sleep: a review of polysomnographic evidence. Behav Sleep Med 2007;5(4):256–78.
[116] Hall M, Vasko R, Buysse D, Ombao H, Chen Q, Cashmere JD, et al. Acute stress affects heart rate variability during sleep. Psychosom Med 2004;66(1):56–62.