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THEORETICAL REVIEW

The resilient brain and the guardians of sleep: New perspectives on old assumptions

Liborio Parrino [a, *], Anna Elisabetta Vaudano [a, b]

[a] Sleep Disorders Center, Dept of Medicine and Surgery, University of Parma, Italy
[b] Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio-Emilia, Italy

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SUMMARY

Resilience is the capacity of a system, enterprise or a person to maintain its core purpose and integrity in the face of dramatically changed circumstances. In human physiology, resilience is the capacity of adaptively overcoming stress and adversity while maintaining normal psychological and physical functioning. In this review, we investigate the resilient strategies of sleep. First, we discuss the concept of brain resilience, highlighting the modular structure of small-world networking, neuronal plasticity and critical brain behavior. Second, we explore the contribution of sleep to brain resilience listing the putative factors that impair sleep quality and predict susceptibility to sleep disorders. The third part details the manifold mechanisms acting as guardians of sleep, i.e., homeostatic, circadian and ultradian processes, sleep microstructure (K-complexes, delta bursts, arousals, cyclic alternating pattern, spindles), gravity, muscle tone and dreams. Mapping and pooling together the guardians of sleep in a dynamic integrated framework might lead towards an objective measure of sleep resilience and identify effective personalized strategies (biological, pharmacological, behavioral) to restore or protect the core properties of healthy sleep.

Human (brain) resilience

Searching the term "resilience" in the title of published material, for the period 1990–2016, the Web of Science (WOS) counts a total amount of 12.171 documents. Psychology and psychiatry related resilience topics are dominant in number (2.064). In contrast, resilience in sleep has been investigated only in a limited amount of studies, equal to 0.28% of all titles. Nevertheless, sleep is a typical resilient system.

"Resilience" is a term taken from the physics of materials, i.e., the property of a material that enables it to resume its original shape or position after being bent, stretched, or compressed. This term was originally applied in the field of ecology and subsequently of social sciences and Engineering. In human physiology, resilience is the capacity of adaptively overcoming stress and adversity while maintaining normal psychological and physical functioning [1].

Research has shown that resilience is ordinary, not extraordinary. People commonly demonstrate resilience [2]. Being resilient does not mean that a person does not experience difficulty or distress. Every individual experiences stressful events but most subjects do not develop related mental disorders such as depression or post-traumatic stress disorder (PSTD), and are thus thought to be "resilient". Recent investigations have identified mechanisms encompassing genetic, epigenetic, developmental, psychological, and neurochemical factors that underlie the development and enhancement of resilience [1]. Factors that predict vulnerability to stress and susceptibility to psychiatric disorders in the face of stress and trauma have also been identified [1]. The active process of responding to challenges, called "allostasis" [3,4], produces adaptation through the hypothalamic–pituitary–adrenal (HPA) axis, the autonomic nervous system, and their interactions with the metabolic system and the pro- and anti-inflammatory components of the immune defense system [4]. The growing understanding of the neurobiology of resilience has significant implications for prevention and treatment of stress-related psychiatric disorders.

The brain represents the central organ of stress and adaptation to social and physical stressors, because it determines what is threatening, stores memories and regulates the physiological as well as behavioral responses that may be damaging or protective [4].

* Corresponding author. Sleep Disorders Center, University of Parma, Via Gramsci, 14, 43126 Parma, Italy. Fax: +39 0521 704107, +39 0521 702693.
E-mail address: liborio.parrino@unipr.it (L. Parrino).

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Abbreviations

AASM	American academy of sleep medicine
ACTH	adrenocorticotropic hormone
ARC	activity-regulated cytoskeleton protein
BDNF	brain-derived neurotrophic factor
CAP	cyclic alternating pattern
CPAP	continuous positive airway pressure
A1	phase A1 subtype of CAP
A2	phase A2 subtype of CAP
A3	phase A3 subtype of CAP
EEG	electroencephalography
EOG	electrooculography
EMG	electromyography
HPA	hypothalamic–pituitary–adrenal axis
ISI	insomnia severity index
KC	K-complex
LTD	long-term depression
LTP	long-term potentiation
NPO	nucleus pontis oralis
NREM	non rapid eye movement
OSAS	obstructive sleep apnea syndrome
PSG	polysomnography
PTSD	post-traumatic stress disorder
REM	rapid eye movement
RBD	rapid eye movement sleep behavior disorder
SEM	standard error of the mean
SOC	self-organized criticality
SWA	slow wave activity
SWRs	sharp wave-ripples
vmPFC	ventro-medial prefrontal cortex
VLPO	ventrolateral preoptic nucleus
WASO	wake after sleep onset
WOS	Web of Science

Brain networking and resilience

In the last decade, the use of advanced tools deriving from statistics, signal processing and information theory has significantly improved our understanding of brain functioning. In particular, connectivity-based methods have played a prominent role in characterizing normal brain organization [5] as well as alterations due to various brain disorders [6]. Graph theoretical methods have been applied to neuroimaging data in order to obtain complementary measures on brain topology, likely reflecting brain organization principles on a more global level. In graph theory, the brain is conceptualized as a complex network of highly interconnected regions [7]. It is defined by a set of nodes with edges between them. In the brain, the nodes are neurons, groups of neurons or cortical regions, and the edges represent anatomical connections (structural brain networks) or dynamical correlations during particular tasks or states (functional brain networks).

Anatomical and functional networks are topologically intermediate between highly regular lattices and random graphs [8]. In other words, brain networks have small-world properties that are a combination of high clustering for local specialization and low path length to enable distributed processing [7,9]. Achard et al. [10] proposed that the resilience of the brain network is due to this small-world architecture. Network attacks experiments have shown high resilience of human functional brain network to both targeted attacks and random errors [11,12]. The conclusion is that "the small-world architecture of the brain confers distinctive benefits in terms of robustness to both random elimination of nodes and selective attack on hubs, and, of course, one can speculate that this robustness might have considerable fitness value in mitigating the loss of network functionality" [10]. As further evidence, modeling studies have shown that neuronal networks will move automatically toward a small-world pattern, due to synaptic plasticity, if left "undisturbed" [13,14]. Such a process might be involved during development, but also – on shorter time scales – during sleep. Graph analyses on scalp electroencephalography (EEG) signals have demonstrated that during non rapid eye movement (NREM) sleep there is a clear tendency to move towards a small-world network organization in all stages and for all the EEG bands, especially for those lower then 15 Hz [14,15]. These findings are important as they represent an empirical validation of the hypothesis of a global and local neuronal plasticity during sleep with related cognitive implications.

Resilience through the critical brain behavior

Recent experimental results, both in vitro as in vivo [16,17], support the idea that the brain operates near the critical point of a phase transition [18,19]. In particular, brain is hypothesized to reach and maintain this critical state by self-tuning its operating parameters toward criticality. This hypothesized framework is named self-organized criticality (SOC) [20]. Criticality can be advantageous for the brain functioning [21], in terms of optimization of dynamical range, information transmission and capacity [22,23]. At the critical point, the neurons can communicate most strongly and over a larger number of synapses [24].

Furthermore, small-world cerebral network topologies display scaling behavior characteristic of criticality [25]. A number of studies have pointed out that information storage [26], computational power [27], and phase synchrony [28] appear to be optimized at the critical point, suggesting a relationship between resilience and critical brain behavior.

While brain criticality during awake resting state has been largely documented, how this behavior modifies in the course of sleep is still a matter of discussion [29,30]. Sleep is hypothesized to regulate the complex organization of brain dynamics [30] by keeping excitatory and inhibitory processes balanced [31]. While prolonged wakefulness increases brain excitability, sleep reduces it, preventing an imbalance towards excitation that would favor uncontrolled runaway activity [31–33]. This theory assigns a fundamental role to sleep in organizing cortical network dynamics towards a critical state, hence assuring optimal computational capabilities for the time awake, i.e., potentiating individual resilience. Sleep disorders, like insomnia and epilepsy, can be due to a deviation from criticality caused by the failure of the adaptive SOC [34,35].

Resilience through sleep

The contribution of sleep to brain resilience can be explored at different levels, moving from theoretical models of neuronal behavior to empirical clinical-based associations between sleep health and resilience [36]. Generally speaking, while a direct influence of lack of resilience on sleep is quite intuitive and largely documented, there is presently much more research published in support of the opposite direction of relationship: that sleep disruption tends to precede and may precipitate the loss of brain

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resilience and consequently may trigger behavioral and emotional-related problems.

Sleep is a typical resilient system and both sleep and resilience actually share similar neuronal networks and crucial brain hubs. The capacity of an individual for resilience, particularly in response to a potent stressor, has been linked to the modulation of ventromedial prefrontal cortex (vmPFC) activity [37]. Similarly, the prefrontal cortex has been implicated in the pathophysiological outcomes of sleep disruption.

The activity of other brain regions, including structures and circuits important for autonomic activation (HPA, the noradrenergic system, serotinergic system, dopaminergic system) and emotion (hippocampus and amygdala) have similarly been linked to both sleep and resilience [38].

Resilience and synaptic plasticity: the role of sleep

Stress can modulate the synaptic plasticity, i.e., the ability of a synapse to change in strength in response to use or disuse. Long-term potentiation (LTP), long-term depression (LTD), and homeostatic scaling of synaptic strength are examples of synaptic plasticity. Activity-dependent synaptic plasticity is considered essential for long-term adaptive changes in behavior, including learning and memory, and the regulation of mood and motivation [39]. Acute stressful events have the capacity to alter long-term synaptic plasticity, by modifying rapidly, although transiently, de novo gene expression and protein synthesis, which are crucial to long-term synaptic changes [40,41]. Among others, Arc (activity-regulated cytoskeleton protein) and BDNF (brain-derived neurotrophic factor) appear to be dysregulated by stress [41]. These genes have been causally linked to LTP and long-term memory [39] and, intriguingly, their transcription appears to be modulated by rapid eye movement (REM) sleep [42].

While stress may disturb sleep, in turn, sleep loss prior to stress exposure may affect the resilience of stress response and potentiate the cognitive consequences of stressful experience. After focal cerebral ischemia, disturbed sleep alters axonal sprouting, expression of synaptophysin, and the ischemia-stimulated neural and vascular cell proliferation in rats [43], hence demonstrating a role of sleep in the modulation of recovery processes and neuroplasticity after acute traumatic injury. At biological level, REM and NREM sleep impact on synaptic plasticity by modulating the transcription and translation of genes involved in molecular biosynthesis and transport, then potentiating existing synaptic transmission and promoting morphological synaptic changes including de novo synaptic formation [39]. According to the model of Tononi and Cirelli [44,45], synaptic strengthening during wakefulness occurs via LTP-like mechanisms, while NREM slow wave activity (SWA) induces mechanisms of LTD or depotentiation throughout the cerebral cortex. In addition to SWA, phasic sleep events, like hippocampal sharp wave-ripples (SWRs) and thalamo-cortical sleep spindles have been suggested to actively take part in synaptic plasticity mediated by sleep through bursts of local protein synthesis that consolidate synaptic modifications and memory formation [46].

Sleep and resilience: clinical evidence

Good sleep is essential to good health. Simply speaking, without sleep or with poor sleep, we become tired, irritable, and our brain functions less efficiently. After a good night's sleep, brain and body feel refreshed and we are restored to normal function. The importance of a good sleep for human health has been largely documented. In the US, promotion of healthy sleep has become a primary objective of Healthy People 2020, a program initiated by the US Department of Health and Human Services aimed at identifying and prioritizing the nation's leading health promotion and disease prevention goals [47]. Sleep disturbance and disruption are risk factors for the development of medical conditions, including mental disorders, both in adults and children [48,49]. One of the most productive fields of research on the relationships between sleep and psychiatric conditions is found in the studies on post-traumatic stress disorder (PTSD). Among patients who develop PTSD after trauma, around 80–90% will suffer from insomnia, nightmares and sleep-disordered breathing compared to a significant lower proportion of individuals who do not develop PTSD [49]. Improving the sleep disorder leads to attenuation of the PSTD symptoms. Recently, Orr and colleagues demonstrated a link between obstructive sleep apnea disorder (OSAS) and PTSD [50]. They found that effective treatment of the respiratory dysfunction by means of continuous positive airway pressure (CPAP) would reduce PTSD symptoms in those subjects with concurrent OSA. Furthermore, improvement was also seen in measures of sleepiness, sleep quality, and daytime functioning, as well as depression and quality of life. Overall, the literature suggests that disturbed REM or non-REM sleep following trauma exposure predict later PTSD as well as other psychiatric outcomes including major depression, other anxiety disorders, and substance use disorders [51,52]. Interestingly, there is a growing body of evidence that suggests the importance of individual difference in sleep characteristics (REM and non-REM) and their disruption as markers of vulnerability to poor psychiatric outcomes following trauma exposure or alternatively, of resilience [53]. The fact that sleep disturbances preceding or following traumatic experiences contribute to poor psychiatric outcomes offers new strategies for prevention and early detection efforts in high-risk populations and individuals exposed to traumatic events.

The guardians of sleep

In the Interpretation of Dreams, Freud claims that when we sleep, the “watchman of our mental health” goes to rest, even if his slumber is not deep [54]. However, the healthy sleeping brain relies on multiple adaptive options that represent the sentinels of a restorative night. Fig. 1 summarizes the proposed guardians of sleep that will be discussed in the following paragraphs.

Artistic masterpieces, such as Constantine's Dream painted by Piero della Francesca in Arezzo (Fig. 2), can offer a symbolic narrative of sleep-protection mechanisms which are not removed when we doze off, but continue to operate intensively during the night. On the eve of the Battle of the Milvian Bridge, Constantine has a vision assuring him of victory in the name of the Christian God if the army moves under the sign of the Cross: “In hoc signo vinces”. The Emperor lies asleep inside his large tent. Three sentinels protect his rest. Three different guardians of sleep, three different ways to accompany Constantine's sleep in his unconscious nocturnal journey. Three watchmen that recall three major characters of the sleep software universally known as the homeostatic, the ultradian and the circadian processes: three topical components of sleep resilience.

Homeostatic process

SWA (EEG spectral power in the 0.75–4.5 Hz range) is a physiological marker for NREM sleep intensity and serves as an index of sleep homeostasis [55]. The decline of SWA across consecutive NREM sleep episodes is predominantly exponential [56]. In addition, mean SWA increases as a function of prior wake duration, especially in the first NREM sleep episode [44]. These dynamics are captured in the homeostatic process S of the two-process model of sleep regulation, which represents the accumulation of sleep pressure (propensity) during waking and its dissipation during sleep [45,56]. According to the synaptic homeostasis theory [44],

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Fig. 1. Schematic representation of the guardians of sleep resilience detailed in the main text.

uptake of information and encoding activity during wakefulness are associated with widespread synaptic potentiation, i.e., an upscaling of net synaptic strength, whereas sleep is associated with the global downscaling of synaptic strength. Process S reflects the increased overall strength of connections in the synaptic network, because the amplitude of SWA is particularly high at the beginning of the sleep period. Simultaneously, EEG slow waves represent a mechanism for downscaling, because the repeated sequence of widespread membrane depolarization and hyperpolarization favors processes of synaptic depotentiation and depression in the network [57].

Circadian process

Any biological process that displays an endogenous, entrainable oscillation of about 24 h is circadian. The 24-h rhythm is driven by a circadian clock, and has been widely observed in plants and animals. The alternation between night and day revolves around the cosmogenetic contrast of deep darkness separated from bright light.

Although circadian rhythms are self-sustained, they are adjusted (entrained) to the local environment by external cues called zeitgebers that include temperature.

In hibernators, torpor represents a way for conservation of energy [58]. In these mammals, periodic arousals to euthermia during torpor occur of on a regular basis. Continuous EEG studies have revealed intense sleep (high amplitude slow-wave activity) immediately following arousals [59]. In humans, body temperature starts falling with sleep onset and declines progressively reaching its lowest point in deep sleep [60]. During NREM sleep the thermoregulatory set point is reduced, enabling body temperature to be adjusted to a lower level. If the drop in operative temperature is too great, arousal occurs tending towards a restoration of waking regulatory mechanisms. In REM sleep, on the other hand, there is evidence that thermoregulation is impaired [60].

Ultradian process

Human sleep is characterized by the regular alternation of NREM and REM sleep developed in four to six 90-min ultradian cycles. These two states of sleep, evidenced by specific EEG, electrooculography (EOG) and electromyography (EMG) codes, compete during the night supported by specific interaction of neuronal systems, which produce specific differences in spectral rhythms predominance. The transitions to and from REM are regulated by two opposite biochemical systems operated by two populations of neurons: REM-on and REM-off [61,62]. The ultradian process is highly-resilient in certain sleep disorders. In untreated severe OSAS, the homeostatic process-S is lacking, shown by the robust decrease of deep NREM sleep. On the contrary, an ultradian cyclicity is clearly outlined by the waxing and waning pattern of arousal sequences closely related to the recurrent REM sleep periods [63].

Are other guardians acting during sleep?

The arousal conundrum

In 1992, the American Sleep Disorders Association established that EEG arousals are markers of sleep disruption representing a detrimental and harmful feature for sleep [64]. For this reason they were excluded from the conventional staging procedures.

A number of studies have established that spontaneous arousals are natural guests of sleep and undergo a linear increase along the life span following the profile of maturation and aging [65]. Moreover, the spectral composition of arousals and their ultradian distribution throughout the sleep cycles reveal that arousals are endowed within the texture of physiological sleep under the biological control of REM-on and REM-off mechanisms. This approach emphasizes the role of arousal in the dynamic structure of sleep [66]. In other words, arousal is not merely a disturbance of sleep, but an integral part of sleep regulation.

The process of arousal is a means by which an organism becomes more alert and more able to respond effectively to danger, whether it be external or internal and whether actual or perceived. The ability to wake up or arouse from sleep represents an enormously important primary defense mechanism. Accordingly, arousals can be considered as guardians of sleep. Imagine what happens at the end of a sleep apnea. Arousals restoring respiratory

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Fig. 2. Costantine's Dream by Piero della Francesca (Arezzo, Italy). Inside his large tent, the Emperor lies asleep guarded by three sentinels: a seated servant, without arms, watches over him and gazes dreamily out towards the onlooker. The other two soldiers stand on guard with different robes and armor.

muscle activity and upper airway patency after sequential apneic episodes are the most powerful life supports during sleep. No arousal means no survival. In terms of sleep, however, arousals do not refer only to waking up, but also to physiological responses in the EEG and to changes in autonomic balance reflected in alterations in heart rate, blood pressure, finger plethysmography and skin potential [66]. Rather than simple "short awakenings", arousals may be considered as different states of the brain, a phenomenon that reflects the negotiation between two main contradictory functional necessities: preserving the continuity of sleep and maintaining the possibility to react [66,67].

K-complexes and delta bursts

The K-complex (KC) is a bi-triphasic EEG slow wave consisting of an initial rapid negative component and a successive positive wave. It lasts >0.5 s with a frequency of 1 c/s, single or in series. The amplitude is >75 μV with maximum expression at the vertex [68]. KC is a major EEG feature of NREM stage 2. According to De Gennaro and collaborators, KCs are forerunners of delta oscillations (1–4 Hz), which are most common during the deepest stages of slow-wave sleep [69].

The physiological significance of KC has been the subject of significant debate. On the one side, KCs are arousal-related phenomena being supported by accompanying activation patterns such as an increase of heart rate and phasic increases in muscle tone. However, the fact that KC activity mirrors other slow waves in NREM sleep supports the idea that KC is a promoter of sleep. Halasz emphasizes the KC's Janus-faced' dual properties, constituting twin homeostatic and reactive functions of NREM sleep [70]. In other words, the KC embodies an arousal with subsequent sleep guarding counteraction that might on one hand serve monitoring of the environment with basic information processing and on the other hand protect continuity of sleep and thus its restoring effect. According to this view, during KC the brain conducts low level cognitive processing to investigate the saliency or possible threat of external and internal stimuli and decides "not to wake up," compensating the disturbing effect of the incoming stimulus by producing a KC [71]. A recent study showed a drastic decrease of KC density (more than 40%) during stage 2 NREM in patients with Alzheimer disease compared to healthy controls [72]. KC density decreased mainly over the frontal areas and the reduction was related to the cognitive decline [72].

Cyclic alternating pattern (CAP) and the guardians of Constantine's dream

In the middle of the 1980s, Terzano and co-workers [73] recognized a micro-structural cyclicity in NREM sleep. They claimed that periodic activation patterns with an interval of 20–40 s constitute an important part of sleep, forming input-associated alternations of activation (A) and background (B) periods. Sensory input activates A phases when applied in B periods in the same way as they appear spontaneously. If we consider the biological function of CAP, its role as an 'instability marker' seems to emphasize something which belongs rather to pathology than physiology. However, in terms of resilience, the CAP system can be viewed as a short range homeostatic process in which the amount of slow wave activity is buffered instantly (fast homeostatic reaction), therefore preserving sleep continuity: a natural "slow wave injection," protecting sleep against perturbations [66].

Activations during sleep are not homogenous. Using intracerebral recordings in drug resistant epileptic patients, Peter-Derex and colleagues analyzed EEG activity during spontaneous or nociceptive-induced arousals in NREM and REM sleep [67]. At the thalamic level, arousals were stereotyped, characterized by a decrease in all frequency bands during NREM sleep, and by a selective reduction of delta-to-sigma bands during REM sleep. At the cortical level, a marked heterogeneity in activation patterns was observed, mainly depending on brain structure and sleep stage. A brief increase in delta power at the beginning of the arousal suggested a temporal dynamic of deactivation/activation/deactivation to return back to sleep at the end of the arousal.

The paradoxical increase of slow activity associated with EEG activation has already been described by the A subtypes of CAP and reflect manifold neural mechanisms for NREM sleep maintenance [74]. According to the distribution of slow and fast EEG frequencies, the A phases of CAP are classified in three forms: A1, A2 and A3 [74]. A1 subtypes have purely slow wave constituents (KCs and slow wave groups) with little autonomic and muscle concomitants. A3 are equal to the traditional arousal pattern with desynchronized fast activity, autonomic signs, and increases in muscle tone. They correspond to the periods of transient activation described by Scheiber et al. [75]. A2 present a mixture of A1 and A3 features, usually beginning with slow waves and followed by the arousal pattern. The time series distribution of phase A subtypes is connected with the homeostatic, circadian and ultradian mechanisms

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of sleep regulation. In particular, subtypes A1 are the expression of slow wave sleep propensity and follow the exponential decline of the homeostatic process. On the contrary, subtypes A2 and A3 are forerunners of REM sleep [70,74]. Due to their dynamic properties and close relation to the structural organization of sleep, the three subtypes of CAP recall the three sentinels of Constantine's dream (Fig. 2).

The three phase A subtypes of CAP undergo quantitative adjustments when sleep is perturbed and across the life-span and in the different sleep pathologies. In healthy individuals, the amounts of CAP phases A1 and A2 increase proportionally under increasing sound pressure levels when white noise is applied, while CAP phases A3 remain unmodified. Therefore, the increase of reactive slow wave rate seems to be proportional to the degree of sleep perturbation by external sound [65]. In normal young adults, subtypes A1 represent 61% of all A phases, an amount that drops to 46.6% in healthy elderly individuals. Conversely, A3 subtypes rise from 10.7% (young adults) to 18.1% (elderly) [74]. In the light of fast homeostatic protection, the reciprocal changes of phase A subtypes from young adulthood to senescence reflect a declining age-related resilience of NREM sleep [76].

Compared to healthy sleepers, in patients with periodic myoclonus, phase A enhancement is limited to subtypes A2 and A3 [77]. Based on wavelet energy and entropy analysis of CAP parameters, insomnia sleep recordings present a longer duration and a higher EEG complexity of B phases between successive A1 subtypes during the build-up phases of slow wave sleep. Moreover, A3 subtypes show an increased duration and a more irregular structure [78]. The variety of sleep microvariations and macrostates is dramatically reduced in severe OSAS where only A3 subtypes of CAP, superficial NREM sleep and fragmented REM sleep can be scored on the polysomnography (PSG) recordings [79]. In contrast, when regular breathing is re-established by effective CPAP, even the sleep system recovers a normal function. However, the different macro- and microstructural components of sleep do not reinstate physiological values simultaneously but follow different steps at different time intervals (Fig. 3) [63,79].

The emerging picture is a combination of fragilities and adaptive strategies in which CAP components play a topical role. Whenever sleep continuity is menaced, whatever the source of perturbation, the brain exploits all the available options. The final microarchitecture of a night of sleep reflects the dynamic balance between the internal constraints and the functional adaptability of the sleeping brain to the ongoing circumstances. With its A phases and with its role of flexibility, CAP is one of the major guardians of NREM sleep.

Intracycle dynamic regulation

Besides CAP, the intracycle dynamic regulation of NREM sleep plays a major role in brain resilience during sleep. When the homeostatic pressure is high, it drives the hypothalamic sleep-promoting neurons to high level of firing, which keeps the wake-promoting arousal system under inhibition [80]. This allows the thalamic burst-firing system to produce spindling and slow wave oscillations. In this condition, sensory input fuels phasic SWA reflected by the phase A1 subtypes of CAP, providing slow wave injections to each perturbation of sleep (instant homeostatic regulation) during the descending slopes of the sleep cycle. When the homeostatic pressure decreases (synaptic decay) the firing of the ventrolateral preoptic nucleus (VLPO) declines gradually, reflected by CAP phases A2 and A3, accompanying the sleeper to progressively higher levels of arousal along the ascending slopes of the sleep cycle preparing the next REM period [70,80].

Sleep spindles: shock absorbers

Spindles are defined as waxing-and-waning EEG waves oscillating at a frequency of 11–16 Hz and predominant over central EEG derivations; spindles characterize NREM stage 2, but can also be

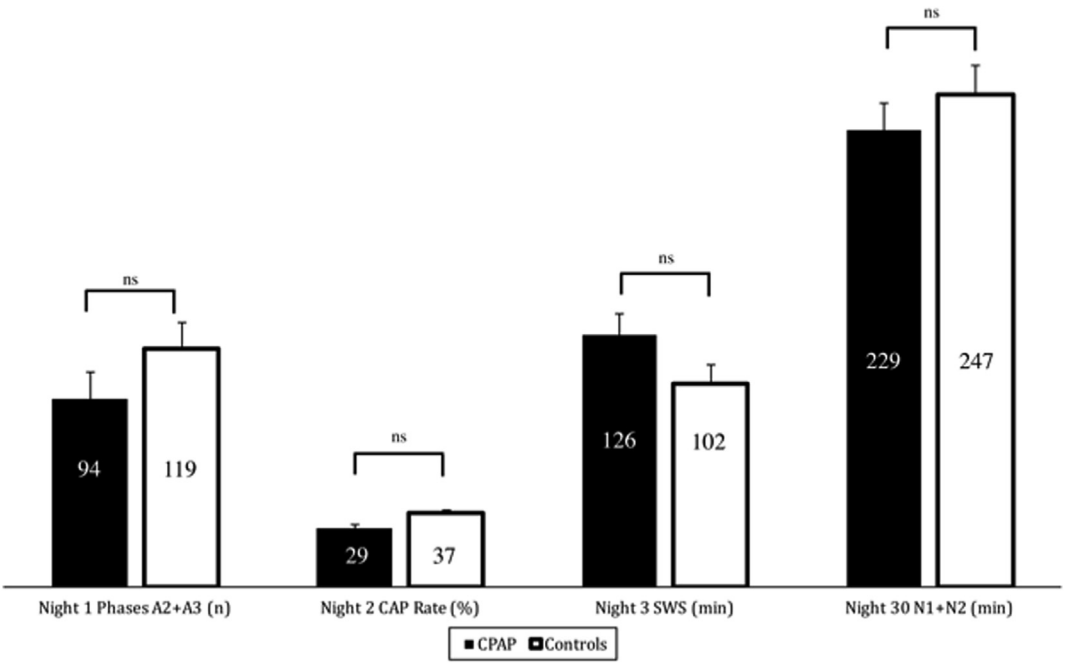

Fig. 3. Representative example of resilient sleep behavior. Patients with severe OSAS under regular and effective CPAP treatment. Recovery of normal sleep parameters at different time intervals after regular and effective ventilatory treatment. Microstructural (phases A2 and A3 of CAP, CAP rate and SWS) and macrostructural (NREM sleep stages 1 and 2) variables are shown. The white bars refer to sleep measures in healthy controls (matched for age and sex), while the black bars illustrate the same measures in OSAS recordings under CPAP treatment. The line above each bar represents the standard error of the mean (SEM). Note that sleep microstructure (phase A2 + A3 in night 1 and CAP rate in night 2) recovers normal values more rapidly than conventional measures of sleep macrostructure (SWS in night 3 and NREM stages 1 and 2 in night 30). The present figure has been extrapolated from the data presented in [63]. n = absolute number; n.s. = non significant difference; SWS = slow wave sleep.

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found during NREM stage 3. Animal and human studies converge to demonstrate that sleep spindles are generated through the interplay between specific populations of thalamic (particularly thalamic reticular) and cortical neurons [81]. According to the model of Steriade [82], sleep spindles rhythm is initiated in gabaergic thalamic reticular neurons, which impose onto thalamocortical neurons rhythmic inhibitory postsynaptic potentials, thus de-inactivating a low-threshold Ca^{2+} current, which promotes burst firing [83]. These bursts are transferred to the cortex that is responsible for generating rhythmic excitatory postsynaptic potentials at spindles' frequency. Spindles generation involves blockage of thalamo-cortical afferents, hence suggesting that they constitute the stones of loss of responsiveness to external stimuli observed during NREM sleep. The "sensory gate" notion assigned to the thalamus and mediated by the spindles, confers a useful role of spindling bursts to preserve sleep continuity by gating sensory inputs. In low spindle-density conditions, the probability of micro-activations/micro-awakenings is higher than in the presence of frequent sleep spindles [84].

In different experimental settings, Halasz and Ujszaszi described a long-lasting post-stimulus inhibition of neural events generating sigma EEG waves [85]. Compared to long-term effects described for evoked KCs, sleep spindle power is not affected by spontaneous KCs for latencies of 5–15 s. These results indicate that the mechanisms underlying spontaneous KCs do not affect spindle power as in the case of evoked KCs [86].

However, a K-spindle response to an arousing stimulus is followed by a more rapid recovery of the baseline EEG pattern, suggesting that spindling activity phasically preserves the sleep state and suppresses activation processes. If the spindle activity gates thalamic afferents to the neocortex, sensory stimulation alters the rhythm of spindles, and this effect is dependent on the modality of the stimuli [87].

Sleep spindles in humans do not prevent arousal reactions to nociceptive stimuli both at surface and intracerebral electroencephalographic recordings [88].

In contrast, tones presented in coincidence with sleep spindles do not activate thalamocortical auditory circuits [89]. Presenting sounds of increasing intensities, individuals with higher spindle density are more likely to preserve the continuity of sleep than subjects with lower spindle density. The ability of individuals with higher spindle density to sleep more efficiently throughout noise might provide them with a better capacity to resist sleep disturbances in response to stress [90].

In a recent study, healthy students were investigated during a period of lower stress at the beginning of the academic semester, along with an assessment of insomnia complaints using the insomnia severity index (ISI) [91]. They completed a second ISI assessment at the end of the semester, a period coinciding with the week prior to final examinations and thus higher stress. To test for the relationship between spindle density and changes in insomnia symptoms in response to academic stress, spindle measurements at baseline were correlated with changes in ISI across the academic semester. Spindle density (as well as spindle amplitude and sigma power), particularly during the first NREM sleep period, negatively correlated with changes in ISI ($p < 0.05$). These results indicate that lower spindle density is associated with a higher vulnerability to sleep disturbances triggered by stress [91].

A dynamic relationship is documented also between KCs, spindles (faster and slower) and theta bursting [83].

Muscle tone during REM sleep: the importance of being absent

In his Interpretation of Dreams [54], Freud claims that the hallucinatory regressions that are activated in the nocturnal site remain harmless because they "are unable to set in motion the motor apparatus by which alone they might modify the external world. The state of sleep guarantees the security of the citadel that must be guarded". In the following decades, experimental investigation ascertained that dreams mainly occur during REM sleep when muscle tone is abolished. Postsynaptic inhibition is the principal process responsible not only for atonia of the somatic musculature during the tonic periods of REM sleep, but also for the phasic episodes of decreased motoneuron excitability that accompany bursts of rapid eye movements during this state [92]. These postsynaptic processes depend on the presence of active sleep-specific inhibitory postsynaptic potentials (IPSPs), which are mediated by glycine. The inhibitory driver originates in the ventromedial medulla and cell groups in this region are activated by a more rostrally located nucleus, the nucleus pontis oralis (NPO), which is located in the pontine tegmentum. Interestingly, basal ganglia structures, such as the substantia nigra pars reticulata and the internal segment of the globus pallidus, have caudal connections to regions that modulate REM sleep atonia [93]. There is also evidence that hypocretinergic axons project to the NPO, as well as the nucleus reticularis gigantocellularis and to lamina 9 of the lumbar spinal cord where spinal cord motoneurons are located. These regions correspond to the brainstem-spinal cord system responsible for the suppression of motor activity that occurs during REM sleep [93].

The motor inhibition that normally occurs during REM sleep is a fundamental property of executive control, as it represents a hinge of behavioral flexibility. During sleep, and especially during the dreaming REM sleep, motor activities are suppressed to prevent the behavioral or alerting consequences of a variety of excitatory stimuli that would otherwise disrupt the sleep state. From an evolutionary point of view, these are obvious advantages to remain quiescent during sleep, especially when the animal is "functionally unconscious". In practice, motor atonia during REM dreaming and reduced muscle tone during NREM stages are sentinels of sleep. Accordingly, when physiological muscle atonia is suppressed, as occurs in REM behavior disorders, abnormal sleep behaviors and unpleasant dreams become the dominant symptomatology [94].

In the general framework upon the role of sleep as a vital need for humans, recent evidence points towards a protecting role of dreams from sleep disruption. This hypothesis would support Freud's original theory on the basic function of dreams. In "An Outline of Psycho-Analysis" indeed Freud states: "a dream is invariably an attempt to get rid of a disturbance of sleep by means of a wishfulfilment, so that the dream is a guardian of sleep" [95]. Recent psychophysiological studies support this view and suggest that especially NREM sleep dreaming protects sleep against external arousing stimulation [96]. This means that the sleep-guarding effect of dreams against arousal is independent of muscle atonia.

Gravity

Recent studies have ascertained that the duration of sleep in astronauts is reduced because they lack one fundamental component of their usual environment: gravity [97]. REM sleep latency and duration are shorter in space suggesting that sleep on ground is due in part to the effort to compensate for the presence of gravity and its effects on the posture and motion of the human body [97].

An interesting interpretation of sleep changes during space flights in humans relies on the reduction of the innate "fear of falling", a complex statement that includes all the efforts during the wake period to maintain the posture of the body and its parts in their natural position. In condition of zero gravity, the risk of fall is reduced and this is instinctively detected by the brain. It is proposed that this explains the fact that REM sleep latency is shorter and total REM sleep time is reduced in space and suggests that in

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weightless environment the need for REM sleep is not as strong as on earth. Like the effect of many other environmental variables such as light, sound and temperature, gravity has a measurable impact on sleep structure and could be hence considered as a "guardian" of healthy sleep.

Conclusion

Under the protection of manifold guardians (dreams, circadian cycle, homeostatic drive, ultradian process, CAP, autonomic arousals, gravity, muscle control) powerful algorithms regulate the autonomy and survival of the sleeping brain. Accordingly, a poorly resilient sleep can be the prelude of adverse health and functional outcomes.

However, in the resilience framework, the relation between health and disease can become a puzzling game. It is known that the activation of the HPA axis and the secretion of cortisol represent an unambiguous indicator of stress [4]. It is also known that sleep, in particular deep sleep, has an inhibiting influence on the HPA axis, whereas activation of the HPA axis or administration of glucocorticoids can lead to arousal and sleeplessness [98]. Accordingly, insomnia is associated with a 24 h increase of adrenocorticotropic hormone (ACTH) and cortisol secretion. Individuals with PSG-confirmed low sleep efficiency and higher values of wake after sleep onset (WASO) have increased cortisol levels, while those with high sleep efficiency do not differ from healthy controls [99]. In practice, sleep fragmentation not only shifts the metabolic balance toward wakefulness but also acts as a resilient response enhancing nocturnal activation of stress-related mechanisms. Sleep disruption can be regarded as both a result of stress and a physiological stressor per se [100].

Human resilience is modulated by several agents including genetic factors, epigenetic–environmental interactions and age-related properties which may be involved in predisposing individuals to sleep disturbance. Whether sleep metrics might be predictive of trait-resilience remains an open challenge. Perhaps, mapping and pooling together the guardians of sleep in a dynamic integrated framework can allow us to define objective measures of sleep resiliece and identify effective personalized strategies (biological, pharmacological, behavioral) to restore or protect the core properties of healthy sleep.

Practice points

- Resilience is the capacity of a system, enterprise or a person to maintain its core purpose and integrity in the face of dramatically changed circumstances.
- It has been proposed that the resilience of the brain network is due to a small-world architecture.
- Self-organized criticality is how the brain operates near a phase transition. At the critical point, the neurons can communicate most strongly and over a larger number of synapses, optimizing information storage, computational power and phase synchrony.
- Sleep disorders, like insomnia and epilepsy, can be due to a deviation from criticality caused by the failure of the adaptive self-organized criticality.
- The healthy sleeping brain relies on multiple adaptive options that represent the guardians of a restorative night.
- The circadian, the ultradian and the homeostatic processes are guardians of sleep as well as dreams, muscle tone atonia, gravity, arousals, k-complexes, spindles and CAP parameters.

Research agenda

- Revisiting sleep disorders under the unifying approach of resilient mechanisms and nocturnal watchmen could be an intriguing challenge.
- Considering the weight of the single guardians of sleep (sleep duration, slow-wave activity, CAP parameters, spindles density, etc) the definition of a sleep-related resilient score index could be hypothesized.
- Implementation of the list of guardians of sleep, particularly the role of vegetative (metabolic, endocrine), molecular, cellular genetic and epigenetic components, environmental (mattresses, clothes, etc), psychological, and social factors is recommended.
- Different scales that measure resilience in humans are available and some have been validated and translated in different languages. They mainly explore the personal control, tenacity, positive acceptance of change and similar items. These scales have been extensively applied in manifold clinical conditions spanning from painful syndromes to psychiatric diseases, but with limited attention to sleep medicine. Accordingly, measurement of resilience in sleep disorders becomes a natural target for future investigations.
- In order to explore the potential role of critical brain behavior, further studies are recommended to verify whether sleep disorders are determined by significant deviation from the "critical point".
- As CAP is a marker of sleep instability, it would be interesting to link experimentally, the neuronal avalanches with the recurrence of A-phases, particularly subtypes A1, which are basically composed of K-complexes and delta bursts, EEG features endowed with powerful resilient properties.

Conflicts of interest

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

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* The most important references are denoted by an asterisk.

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