Vibha M. Jha · Sushil K. Jha

Sleep: Evolution and Functions

Springer

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निद्रायत्तं सुखं दुःखं पुष्टिः कार्श्यं बलाबलम्।
वृषता क्लीबता ज्ञानमज्ञानं जीवितं न च ॥३६॥

- चरक संहिता, सूत्रस्थान २१

The manifestation of joy & sorrow, health & strength & weakness & manhood, knowledge & ignorance, life & death, all these occur depending on how much sleep one obtains daily.

Charak Samhita
Sutrasthan 21/36

Charak Samhita is a famous book of Ayurveda. It was composed before the second century, and is one of the pillars of ancient Indian medical science.

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Sleep: Evolution and Functions

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To our parents for always loving, supporting, and encouraging us.
And
To our three lovely angels Subhanshi, Suvali, and Sumanvi. You are the three pillars of our life. Without your love and understanding, it would not have been possible to complete this book.
Vibha and Sushil

Preface

Mammalian species, including man, have almost exclusively provided the substrate for evaluating the intricate biological tapestry of sleep. Despite decades of intensive research, the functions and purpose of sleep remain elusive. By evaluating nonmammalian and mammalian organisms with a long evolutionary history may provide insight into our understanding of sleep and its functions. It may offer us some clues to find out the ways for sleep management and skills for our rapidly changing society, where the majority among us are living in a sleep-deficient condition.

The electrophysiological expression of sleep varies across phylogeny. In mammals and birds, there are two well-known, cyclically alternating electrophysiological patterns of sleep. They are characterized as non-rapid eye movement (NREM) sleep having high-amplitude and slow-wave electroencephalogram (EEG) activity with reduced muscle tone. Rapid eye movement (REM) sleep is characterized by a low amplitude (EEG) and rapid eye movements, almost similar to waking, but atonia of skeletal muscle is the hallmark of REM sleep. To date, all studied terrestrial mammals and birds exhibit these two distinct sleep stages. However, the same electrophysiology of mammalian NREM and REM sleep has not been convincingly demonstrated in invertebrates and lower vertebrates. Different electrophysiology in nonmammals, for example, distinctive high-amplitude spike activity in various reptiles, is correlated with behavioral sleep, which disappears in behavioral waking.

The imposition of mammalian sleep criteria on nonmammalian species has led to a significant, long-running controversy in the literature. Do the organisms other than mammals and birds have "true" sleep, or do they manifest significantly different unrelated correlates of sleep/rest? What are the phylogenetic origins of sleep? If this state has perpetuated in phylogeny throughout millions of years, then what does this reveal about the functions of sleep? Why have the phylogenetic and adaptive changes in sleep occurred during evolution? What are the adaptive changes occurring across the life-time, and why would it be? These are some questions that await answers.

Many varied functions have been proposed for sleep, including, among others, the development of neural circuitries, energy conservation, memory consolidation, synaptic plasticity, enhancement of the immune system, brain development, and many more. These functions have been proposed as a result of manipulations such as

acute and chronic sleep deprivation, the effects of pharmacological agents, and genetic manipulations at the cellular level in animals model organisms. A current area of interest that ties these diverse topics together pertains to the understanding of human sleep disorders. In this book, we have attempted to explore the phylogenetic origins of sleep, functions of sleep, and the applicability of these findings to human sleep and treatment of its disorders.

The primary aims of this book are (1) to explore the evolution of sleep behavior from an evolutionary and phylogenetic perspective, (2) to evaluate the proposed functions of sleep utilizing experimental research in a variety of mammalian and nonmammalian species, and (3) to assess how this perspective can lead to a broader clinical understanding of human sleep management and its disorders.

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Sleep: Basic and Historical Aspects

1

Abstract

Sleep is considered a naturally occurring reversible state of rest, which is accompanied by reduced voluntary activity and sensory perceptions. It is involved in the regulation of body physiology and cognitive functions. Earlier it was thought that sleep is generated as a consequence of a mechanical blockage in nerve conduction. This popular concept of that era was disregarded only in the late 1950s after the endorsement of von Economo's findings of 1927 that insomnia and hypersomnia are caused in individuals with lesions in the anterior and posterior hypothalamus. Around the same time, "rapid eye movement sleep" was also discovered, which attracted several ingenious researchers toward the sleep field. Several studies between the early 1960s and late 1970s demonstrated that sleep was generated exclusively by sleep-associated neural circuits. We now know that the wake centers are located in the brainstem, midbrain, and basal forebrain; non-rapid eye movement (NREM) sleep centers are located in the anterior hypothalamus and rapid eye movement (REM) sleep centers are located in the brainstem. We now have a clear understanding of a large part of brain sleep–wake machinery, but, surprisingly, it took a long time to come to this point. Although our ancient traditional science had described some of the modern concepts of sleep, it somehow remained obscured before contemporary researchers provided scientific evidence. This chapter highlights the conceptual and historical aspects of sleep research and the events that led sleep researchers to believe that sleep is not a consequence but a vital physiological state.

Keywords

NREM sleep · REM sleep · REM-2 sleep · Reticular system · Sleep theory

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1.1 Introduction

Sleep, like any other physiological functions, is an essential requirement for the survival of animals. Almost all animals demonstrate a daily recurring period of prolonged rest or a sleep-like state. A consensus on a universal definition of sleep that can express the somnolence behavior of all animals is lacking. With the current concepts, it can, however, best be defined as "*a naturally occurring rhythmic reversible state of rest in all animals accompanied with reduced voluntary activity, sensory perceptions, a typical body posture, and involved in the homeostatic regulation of body physiology, and cognitive functions*."

There has been a long debate on how sleep is generated. In the past, Jan Evangelista Purkinje (1846), Nathaniel Kleitman (1929–1939), Fredric Bremer (1935–1937), and several others proposed that sleep was a passive phenomenon. They offered their views that "sleep is a consequence of a mechanical blockage in nerve conduction." Purkinje proposed in 1846 that sleep is generated primarily because of a functional disruption between the cerebrum and brain stem (Moruzzi 1964). Nathaniel Kleitman reasoned that sleep is inducted if the wakefulness center in the brain failed to remain in a state of continuous excitation (Kleitman 1939, 1964). Similarly, Bremer, in 1935 and 1937, proposed that the sudden withdrawal of a tonic sensory input to the brainstem produces both the electroencephalogram (EEG) and ocular manifestations of sleep (Kerkhofs and Lavie 2000). Nathaniel Kleitman proposed, "any drop of the afferent barrage, following muscular relaxation and closure of the eyes, and an increase of fatigability of the cerebral cortex and the subcortical structures involved in wakefulness would lead to a state of functional deafferentation of the cerebral cortex. This state would cause sleep merely because it is incompatible with wakefulness" (Kleitman 1939; Moruzzi 1964).

On the other hand, von Economo, a Viennese neurologist, did not agree with the disconnection theories as he noted in his clinical observations between 1917 and 1929 that insomnia and hypersomnia are caused in individuals with lesions in the anterior hypothalamus and of the ascending arousal pathways at the midbrain–diencephalic junction, respectively (Lavie 1993). Nauta, in 1946, offered similar evidence from rat experiments that sleep is induced by an inhibitory action on the waking areas by sleep-related neural population (Nauta 1946). Von Economo and Nauta provided the first experimental basis that the hypothalamus is the main sleep–wake regulating area in the brain (Lavie 1993; Nauta 1946). The passive theory of sleep was based initially on general belief and perception, but von Economo's and Nauta's findings provided the major scientific foundation of sleep genesis. These observations of von Economo and Nauta ultimately helped in changing the concept that sleep is not a passive phenomenon but an active process generated by well-defined neural circuitries.

1.2 Concept of Sleep in Ancient Indian Science

An ancient Indian science, the "*Ayurveda*," considers sleep to be an essential component for a healthy life (Toolika et al. 2013). Ayurveda describes "sleep and its disorders" in its *Sushruta Samhita* (circa 100 BC–900 AD), *Charaka Samhita (*circa 300–500 AD), and *Vagbhatta* (circa 700 AD) (Kumar and Gulia 2016; Toolika et al. 2013; Trikamji 1997). The Mandukya Upanishad, an ancient Indian text, which is also a part of Atharvaveda, talks about the four different states of consciousness: Jagrat (wakefulness), Svapna (dream sleep), Susupti (deep sleep), and Turiya (a fourth state). The word "AUM" or "OM" and its significance have been described for the first time in the Mandukya Upanishad. It says that "OM," the ultimate brahman, has four quarters: (1) the waking state (Jagrat), (2) the dream state (Svapna), (3) the deep sleep state (Susupti), and (4) the transcendental state (Turiya) (Fig. 1.1). Importantly, Ayurveda also describes a homeostatic balance between three pathophysiological attributes or doshas as the basis of a healthy brain and body (Bhushan et al. 2005). Disturbance in the balance between the *doshas* results in changes in various functions, including sleep, and can lead to multiple sleep disorders (Kumar and Gulia 2016). The dominance of the *vata dosha* is considered

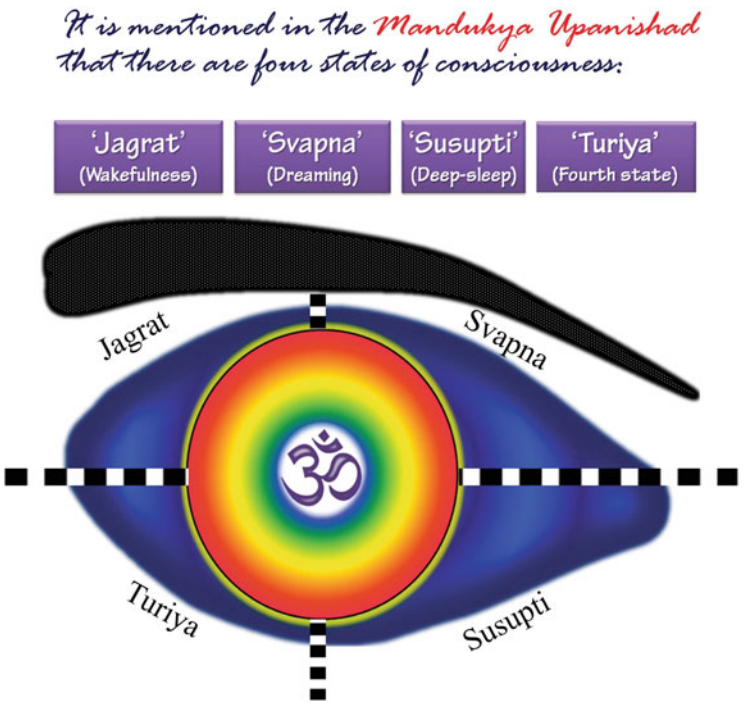

Fig. 1.1 As mentioned in the Mandukya Upanishad, there are four quarters of the word "OM": (1) Jagrat (wakefulness), (2) Svapna (dream sleep), (3) Susupti (deep sleep), and (4) Turiya (a super divine fourth state)

to be associated with increased arousals at night, and daytime sleepiness in elderly subjects with dementia (Chaudhuri et al. 2011). Also, persons of all ages with dominating *vata dosha* may experience poor sleep quality and insomnia (*Charaka Samhita Sutrasthana*) (Madhavan and Vijayan 2017). It is mentioned in *Charaka Samhita Sutrasthana* that persons with the *pitta dosha* have a moderate sleep but might have sleep disturbance because of dreams (Kumar and Gulia 2016; Madhavan and Vijayan 2017). Persons with the *kapha dosha* may sleep comfortably, but they face difficulty in keeping themselves awake (Rao 2002). Finally, those with calm and lazy temperament are more likely to have no difficulty in falling asleep or maintaining sleep. These individuals can be considered to be *kapha dosha*-dominant, as calmness and lethargy are linked with the *kapha dosha*, which is also associated with daytime sleepiness (*Charaka Samhita Vimanasthanam*) (Rao 2002). Therefore, the ancient Indian scriptures had described sleep without and with a dream, much before the characterization of sleep as NREM and REM sleep by modern science.

Another interesting fact worth mentioning is that milk is considered as an exceptional and unique part of a nutritional diet in Ayurveda. Completely digested milk in the body nourishes all tissues, boosts positive emotions, and plays an essential role in balancing all doshas. A homeostatic balance between all three doshas is the basis of having a healthy brain and body, including good quality sleep; therefore, warm milk consumed a couple of minutes before bedtime may facilitate quality sleep. To drink a glass of warm milk before bedtime has been in practice for a long time in Indian culture. Recently, it has been reported that milk and dairy product consumption enhances sleep quality (Yasuda et al. 2019). Milk is rich in tryptophan, an essential amino acid, and a precursor of several vital biomolecules such as serotonin, melatonin, and tryptamine (Nongonierma and FitzGerald 2015). Tryptophan is converted into 5-hydroxytryptophan, which is further converted into serotonin and melatonin. Melatonin acts as a hormone and is released from the pineal gland during the night. It plays an essential role in sleep induction (Lemoine et al. 2007; Luthringer et al. 2009). Melatonin is primarily synthesized in the pineal gland from tryptophan. The pineal gland is situated outside the blood–brain barrier. Hence, it captures tryptophan rapidly from the blood (Pereira et al. 2017). Moreover, tryptophan and other amino acids compete for the same transporter to enter the brain, so it becomes difficult for tryptophan to pass through the blood–brain barrier. As a result, less tryptophan is available for serotonin synthesis in the dorsal raphe, which is currently considered as a wake inducer (Pereira et al. 2017).

In the 1970s, serotonin was considered as a sleep inducer. This hypothesis was, however, proven wrong in the 1980s and 1990s. Dahlstrom and Fuxe in 1964 reported that large lesions in the serotonergic neurons of the ponto-mesencephalon in the cat induced long-lasting insomnia (Dahlstroem and Fuxe 1964). It was then proposed that lasting insomnia was primarily because of the decreased serotonin level in the cortex (Dahlstroem and Fuxe 1964). Later, it was found that serotonin restored sleep in *p*-chlorophenylalanine (PCPA)-induced insomniac cats (Denoyer et al. 1989). Para-chlorophenylalanine is a blocker of tryptophan hydroxylase enzyme, which is involved in serotonin biosynthesis from tryptophan (Koe and

Weissman 1966). It was proposed that PCPA microinjection might have depleted serotonin level; hence, its restoration through the exogenous application of 5-HT rescued sleep in insomniac animals (Denoyer et al. 1989). As a result, the serotonergic theory of sleep was proposed. However, this theory was soon proven wrong, as it was found that serotonin and serotonergic neurons in the dorsal raphe are indeed closely linked to the generation of wakefulness (Ursin 2002). Michel Jouvet has mentioned in one of his articles about the relationships between serotonin and sleep like a favorite love story, that is, first an encounter of a biomolecule without a face (1955–1963), thereafter the honeymoon phase of serotonin theory of sleep (1964–1973), followed by a divorce because serotonin was discovered as a wake inducer (1975–1985). Jouvet, though, said that the story of sleep and serotonin had not yet gone into the graveyard (Jouvet 1999). It has been reported that serotonin helps induce EEG slow-wave activity in human sleep (Seifritz et al. 1996), and PCPA-mediated insomnia does not alter sleep regulation and instead produces hyper-responsiveness (Tobler and Borbély 1982). Sleep-promoting effects of serotonin have also been found in *Drosophila* (Yuan et al. 2006). Therefore, the sleep theory of serotonin is still an unresolved story and needs to be revisited with precaution.

1.3 The Journey of Sleep Theory

Nathaniel Kleitman, in 1939, proposed an evolutionary and ontogenetic theory of sleep–wakefulness (Kleitman 1939, 1964). His approach was based on the observations of wake patterns in young organisms and the organisms having large cortical lesions. He observed that such organisms experienced long sleep and were getting awakened only for their needs, such as food and water. Kleitman referred to the wake pattern in the absence of cortex as "wakefulness of necessity." He proposed a new pattern "wakefulness of choice" that gradually evolves with the development of cortex (Finger 1994; Kleitman 1939, 1964). He was initially a proponent of the passive theory of sleep as he viewed sleep as an outcome of cessation of wakefulness (Kleitman 1939, 1964). However, he changed his view when another sleep state, "rapid eye movement (REM) sleep," was discovered in 1953 from his laboratory at the University of Chicago. Eugene Aserinsky, a Ph.D. student of Nathaniel Kleitman, noticed that people exhibited rapid and jerky eye movement during sleep. The EEG recordings showed that brain activity during periods of eye movement was closer to an awake condition, and the breathing and heart rates were also high during the period of jerky eye movements (Aserinsky and Kleitman 1953). They noticed that when majority subjects awakened from the phase of "rapid, jerky, and binocularly symmetrical eye movements" sleep, they were able to recall the most vivid and elaborate dreams. Interestingly, subjects awakened from the sleep of ocular quiescence failed to remember their dream (Aserinsky and Kleitman 1953). Thus, he named this stage of sleep with visual activity as sleep with rapid eye movement (REM) periods, although initially, he intended to call it as sleep with jerky eye movement periods or JEM periods (Aserinsky 1996).

Frederic Bremer was another pioneering researcher who changed his dominating view that sleep is a passive phenomenon (Bremer 1977; Gottesmann 1988; Kerkhofs and Lavie 2000). In a transection study, he demonstrated that the area for wake regulation is located in the brainstem (Bremer 1977; Gottesmann 1988; Kerkhofs and Lavie 2000). In his findings, he observed that a transection at the brainstem colliculi (cerveau isolé) induced continuous sleep, whereas the animal was able to maintain wakefulness at lower brainstem area transection (encephale isolé). The sleep-like behavior, along with slow cortical waves, almost convinced him that sleep was a passive phenomenon, which was resulted from cortical deafferentation. Frederic Bremer was an outstanding experimenter and performed all of his experiments by himself. However, after the Hess findings and discovery of the ascending reticular activating system and REM sleep, he realized that he had wrongly interpreted his experimental results (Kerkhofs and Lavie 2000).

Although REM sleep discovery in 1953 was a landmark event in the field of sleep research, it could not effectually break the dominating concept of the era that sleep is a passive phenomenon, which appears due to the cessation of wakefulness. Michel Jouvet's findings from the University of Lyon, France, between 1959 and 1961 that REM sleep emerges from the caudal brainstem activity (Jouvet 1961) changed the era old dominating concept of passive sleep theory. In a series of experiments, his group demonstrated that (1) REM periods are also present in the cat; (2) both cats and humans show slight muscle tension and low brain activity during slow-wave sleep; (3) the postural muscles become completely inactive during sleep of REM periods; (4) appearance of REM sleep can be altered by systemic administration of a cholinergic agonist and antagonist; and (5) the REM sleep-like state can be induced with the electrical stimulation of the caudal mesencephalic region or pontine tegmentum brainstem areas (Jouvet 1962; Jouvet and Michel 1960). He called it a "paradoxical sleep stage" as the brain was active, but the bodily movements were subdued. The animals showed periodic loss of neck-muscle tone (muscle atonia), jerks in the paws and tail, rapid eye movements, rapid breathing movements along with arrhythmias, and increased arousal thresholds by auditory and reticular stimulation (Jouvet and Michel 1959; Jouvet et al. 1959). Dement and Kleitman proposed that sleep propensity during REM periods was intermediate between wake and sleep (Dement and Kleitman 1957), but it was Jouvet's group who demonstrated that paradoxical or REM sleep was the deepest state of sleep, although he has used deep sleep terminology for slow-wave sleep (Jouvet et al. 1959).

Currently, the vigilant states in the polysomnographic recordings of mammals and birds are characterized as wakefulness, NREM, and REM sleep. Sleep stages are usually scored by partitioning a sleep recording into nonoverlapping epochs of equal length. A single sleep stage is assigned for each epoch. If more than one sleep stage occurs within an epoch, the sleep stage that takes up the most significant portion in the epoch is scored as the stage for the whole epoch. Usually, vigilant states are scored in 4-s epochs in rats and mice and 30-s epochs in cats, dogs, and humans. The epochs of low-voltage and high-frequency waves with desynchronized EEG associated with the increased motor activity are characterized as awake. The epochs of high-voltage, low-frequency waves, synchronized EEG with prominent delta

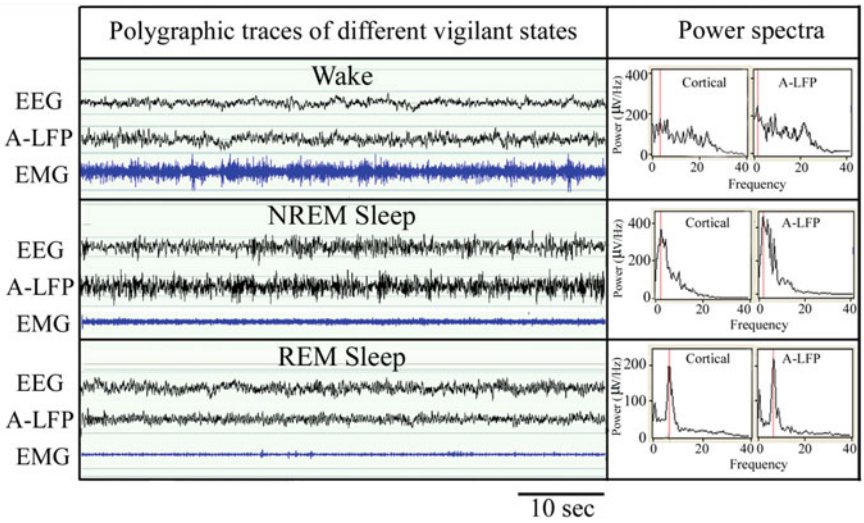

Fig. 1.2 Polysomnographic traces along with the power spectral profile of cortical EEG and local field potential (A-LFP) during wakefulness, NREM, and REM sleep in the rat. (Taken from Tripathi et al., Front. Behav. Neurosci, 2018)

waves, and decreased motor activity relative to the waking are considered as NREM sleep, while low-voltage, high-frequency waves, desynchronized EEG with a prominent theta peak, and nuchal muscle atonia are characterized as REM sleep (Fig. 1.2).

1.4 Does the Discovery of "REM-2" Sleep Suggest a Dual Nature of REM Sleep?

We discovered another REM sleep stage in a phylogenetically ancient mammal "the ferret" (*Mustela putorius furo*), which has been named as "REM-2" sleep. Marks and Shaffery observed the "REM-2" sleep state in the ferret for the first time in 1996. They characterized the "REM-2" sleep state by a REM sleep epoch along with sensorimotor rhythm in the ECoG. They found in the spectral analysis a slowing of the theta rhythm in REM-2 episodes. Furthermore, they recorded sleep–wakefulness in two ferrets only and scored 6.4% "REM-2" sleep state in one animal, while 37% in another animal (Marks and Shaffery 1996). We, however, observed $3.42 \pm 0.98\%$ "REM-2" in eight animals (Jha et al. 2006). In our study, the occurrence of REM-2 was consistent and varied by only around 3% in all eight animals. In REM-2, we observed a mixture of high-voltage and fast-wave EEG activity, which initially appeared similar to the NREM and REM sleep "transition state" (Tr) (Fig. 1.3). However, when we analyzed EEG power spectral with caution, it appeared to be significantly different from the NREM to REM sleep transition state. For example, when we normalized REM-2 and Tr epochs to NREM sleep "theta activity," the Tr

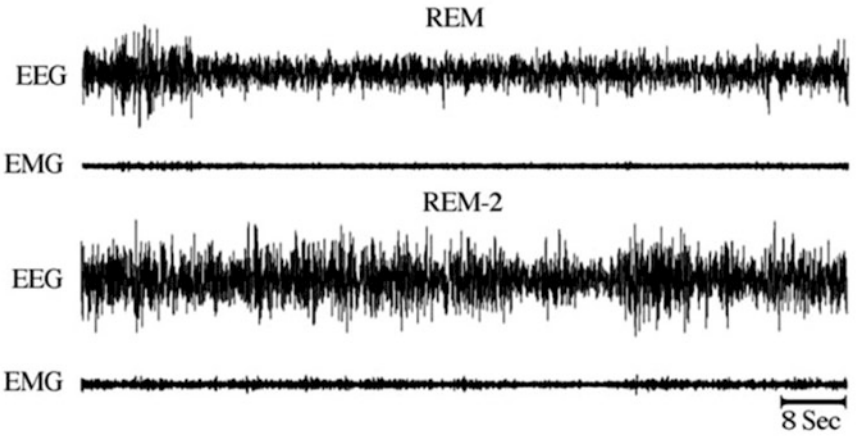

Fig. 1.3 Representative EEG/EMG polygraphic traces in REM and REM-2 sleep states in the ferret. (Taken from Jha et al., Behavioural Brain Research, 2006. Permission obtained from Copyright Clearance Center of BBR for reproduction of the Fig under license # 4835301248808)

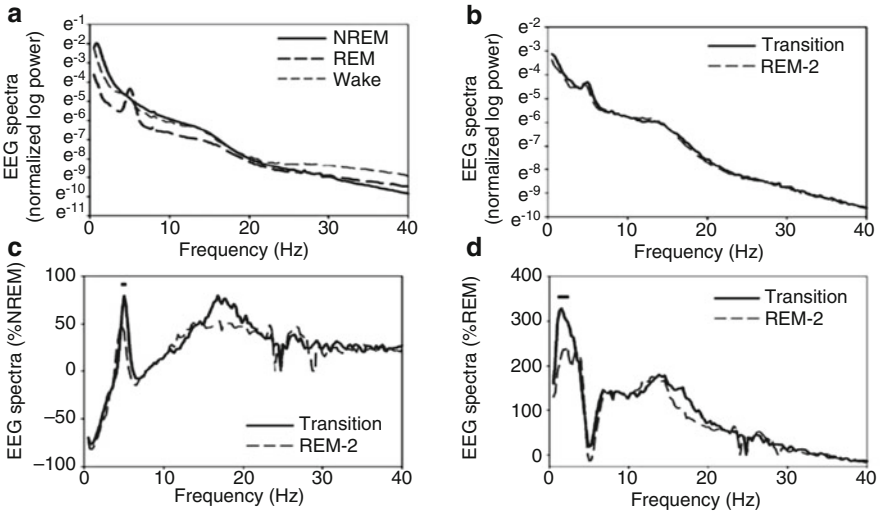

Fig. 1.4 EEG spectral profile during (**a**) wake, NREM sleep, REM sleep, and (**b**) transition and REM-2 sleep in the ferret. EEG spectral profile during the transition and REM-2 stages normalized to (**c**) NREM sleep and (**d**) REM sleep. A black colored bar in panels (**c**) and (**d**) indicates significant difference between transition and REM-2 ($p < 0.05$, repeated measures one-way ANOVA). (Taken from Jha et al., Behavioural Brain Research, 2006. Permission obtained from Copyright Clearance Center of BBR for reproduction of the Fig under license # 4835301248808)

epochs had greater peaks at faster EEG frequencies than in REM-2 (Fig. 1.4) (Jha et al. 2006).

Similarly, when Fourier-transformed REM-2 and Tr epochs were normalized to REM sleep, Tr epochs contained significantly higher amounts of SWA with peak

energies of approximately 1–2 Hz slower than observed in REM-2 (Jha et al. 2006). In addition, we found that REM-2 did not always occur at the borders of REM and NREM sleep as would be expected if this was simply a REM–NREM transition (REM-2 to REM sleep 57.71% of all transitions; REM-2 to NREM sleep 24.22% of all transitions), and REM-2 bouts were significantly more prolonged than Tr (Jha et al. 2006). The "REM-2" sleep state has not been reported in platypus or any other phylogenetically ancient mammals, suggesting (1) a dual nature of REM sleep in some mammals and that (2) the REM-2 sleep state could be evolutionarily, a new REM sleep state.

1.5 Sleep Scoring and Characterization in Human Subjects

Approximately 15 years after REM sleep discovery in 1953, the American Academy of Sleep Medicine (AASM) constituted a committee in 1967 under the chairmanship of Allan Rechtschaffen and Anthony Kales to develop the first standardized scoring and characterization method of different sleep stages in healthy adult subjects (Rechtschaffen and Kales 1968). It was popularly known as the "R and K rules" and had been widely used till 2007. It was modified and updated in 2007 and is known as the "AASM scoring manual" (Berry et al. 2012). The "R and K rules" allow characterizing sleep into four stages of non-rapid eye movement (NREM)/ slow-wave sleep (SWS sleep) (stages 1, 2, 3, and 4) and rapid eye movement (REM) sleep as stage 5. The AASM scoring manual, however, adopted the characterization of sleep into four stages: stages N1, N2, and N3 and stage R sleep (REM sleep). In the newly approved method, N1 and N2 stages correspond to S1 and S2 phases of R and K rules, while in the N3 stage, the S3 and S4 phases were merged (Berry et al. 2012).

Before AASM guidelines of 1968, Alfred Loomis had reported (in 1937) about the changes in brain potential in sleep. His group noticed that the changes in the level of consciousness were connected with the changes in EEG waves. He broadly classified vigilant states into five types: (A) Alpha: Alpha rhythm was appearing in trains of various lengths. The eyes were slowly rolling under closed eyelids. (B) Low Voltage: A quite straight record with no alpha rhythm and only the low-voltage potentials were changing. Eyes were sometimes rolling. (C) Spindles: Recording lines were slightly irregular with 14/s spindles of 20–40 μV every few seconds. (D) Spindles plus random: The spindles continued with the large random potentials 0.5–3 per second. The random voltages were as high as 300 μV. (E) Random: The spindles were inconspicuous, but the large random potentials persisted. The random state included irregular as well as occasional fairly regular bursts of slow potentials (Loomis et al. 1937). It is, however, not clear in this paper if Loomis had also included EEG with low potential sleep (a current classification of REM sleep) into stage E-Random. However, it was very clear from his observation that the alpha wave stage was awake state (Loomis et al. 1937). It was so well-found that even in today's time different tools and EEG feature extraction algorithm corroborate such findings that alpha activity remains predominantly present in relaxed subjects with

closed eyes, which plays an essential role in perceptual awareness and pleasant feeling (Brown 1970; Laufs et al. 2003).

In humans, the EEG in wake shows a desynchronized pattern along with mixed beta and alpha activities. EMG remains relatively high, and the EOG shows eye blinking and rapid movements. As the subject becomes drowsy and closes his eyes, the EEG shows predominant alpha activity with reduced EMG activity and slow rolling eye movements (SREMs). From wakefulness, the subject typically proceeds to stage N1. Stage "N1-NREM sleep" is a transitional state characterized by low-voltage, fast EEG activity. Stage "N1-sleep" is scored when more than 15 s ($\geq$50%) of the epoch is made up of theta activity (4–7 Hz). The EMG shows less activity than in the wake stage, and the eyes begin to show SREMs. Stage "N2-NREM sleep" is also termed as sigma, spindle, or intermediate sleep and is characterized by the presence of predominant EEG theta activity (4–7 Hz). The EEG shows minimal alpha activity with increased amplitude. Delta activity begins to appear but occurs in less than 20% of the epoch. The EMG activity remains low. Interestingly, K complexes and sleep spindles start occurring in this stage in a typically episodic manner. The presence of K complexes, with or without sleep spindles, is a hallmark of "N2-sleep." Stage "N3-NREM sleep" is also called as deep sleep or slow-wave sleep (SWS) or delta sleep. SWS is marked by high-amplitude slow waves with a further decrease in muscle tone. Both K complexes and sleep spindles are seen in stage N3 sleep.

EEG epochs with low-amplitude, mixed-frequency EEG, low chin EMG tone, and rapid eye movements are scored as Stage R or REM sleep. This stage is continuously scored in subsequent epochs as stage R if the EEG shows low-amplitude, mixed-frequency activity without K complexes or sleep spindles, and low EMG tone even if rapid eye movements are missing. During REM sleep, the eyes move rapidly under closed eyelids while dreaming, but at times, it remains absent. Therefore, EOG activity is not needed to mark the start of a REM period.

1.6 The Current Concept of Sleep–Wakefulness

The neuronal components involved in the regulation of wakefulness, NREM, and REM sleep are, anatomically as well as functionally, closely interlinked. The sleep–wake circuitries should be regarded as antagonistic systems for the recurring appearance of sleep–wakefulness cycles. The classical experiments by Hess in 1927 and Frederic Bremer in 1935 may be considered as the stepping-stone of experimental research towards understanding the neurophysiological mechanism of sleep–wakefulness. They showed induction of sleep-like behavior by protracted low rate electrical stimulation of the midline thalamus and by transection of the neuraxis at the midbrain level ("cerveau isole" preparation). The pioneering studies by Moruzzi and Magoun and several others showed the role of brainstem reticular formation in wakefulness and alertness. The rostral part of the brainstem reticular system was attributed to alertness and waking, while NREM sleep-inducing areas are located in the anterior part of the hypothalamus (Moruzzi 1972). The sleep-like EEG patterns

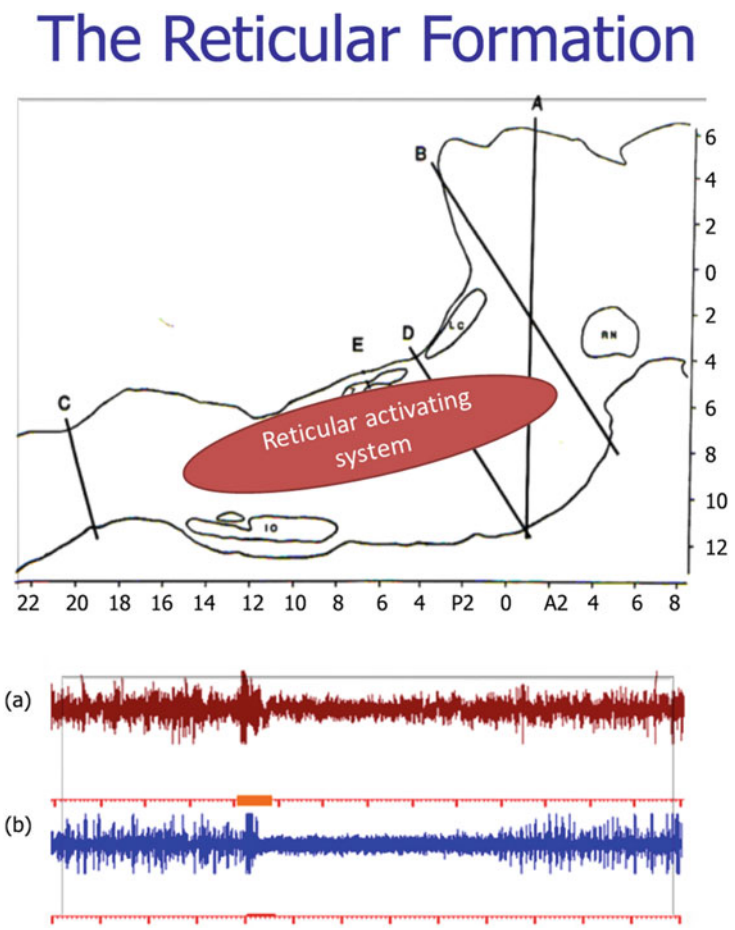

Fig. 1.5 Mild electrical stimulation of the midbrain reticular formation induces EEG desynchronization in (**a**) normally sleeping animal and (**b**) anesthetized animal

of the "cerveau isole" animals were attributed to the withdrawal of influences from the rostral reticular activating system. Thus, it was found that the neuronal substrates involved in the induction and maintenance of waking and sleep are located in the brainstem reticular system and forebrain (Fig. 1.5).

The regulation of wakefulness and sleep is based on coordinated interaction between wake-promoting networks of the upper brain stem and lateral hypothalamus (LH) and sleep-promoting networks of the anterior hypothalamus (AH), which mutually inhibit each other to enable transitions into the respective brain states [for review, see Jha and Mallick 2011]. The wake-promoting network includes mainly the locus coeruleus "noradrenergic neurons," pedunculopontine tegmental and laterodorsal tegmental nuclei "cholinergic neurons," the dorsal and median raphe nucleus "serotonergic neurons," and the hypothalamic tuberomammillary

nucleus (TMN) "histaminergic neurons." These brain areas have widespread projections to the basal forebrain, cerebral cortex, and lateral hypothalamus. Other nuclei present adjacent to the TMN is posterior lateral hypothalamus, which produces "orexin-A and -B." These neuropeptides are also called hypocretin 1 and 2, respectively. These neurons reinforce the activity of wake-promoting neurons. Inhibitory neurotransmitters, such as GABA and galanin, are released mainly from two sleep centers, "ventrolateral" and "median preoptic" nuclei of the hypothalamus, which switch OFF all wake-promoting networks. Furthermore, it has been reported that in some parts of the brain, particularly in the basal forebrain, adenosine (a product of cellular metabolism) accumulates and auto-hyperpolarizes the wake-active neurons, which in turn disinhibit the VLPO sleep-promoting networks. Furthermore, balanced interaction between different brainstem pontine networks mediates the initiation and maintenance of REM sleep. During REM sleep, "REM-ON" neurons of the sublateral dorsal (SLD) region (precoeruleus) become active and initiate REM sleep. During the transition from NREM to REM sleep, disinhibition of REM-ON neurons from the diverse projections such as the periaqueductal gray matter (vlPAG) and the adjacent lateral pontine tegmentum (LPT), VLPO and orexinergic neurons allow the initiation of REM sleep. The noradrenergic LC and serotonergic DRN areas also have REM-OFF neurons, which play an important role from both sides of the "REM sleep switch" in the modulation of REM sleep [for review, see Jha and Mallick (2011)].

1.7 Conclusion

Although ancient Indian science had illustrated some of the modern concepts of sleep, it somehow remained obscured before contemporary researchers provided scientific evidence. Based on general belief and perception, sleep was initially considered a passive phenomenon. Sleep researchers provided a major scientific foundation of sleep genesis. The observations of von Economo and Nauta helped in changing the concept that sleep is not a consequence but a vital physiological state generated by well-defined neural circuitries. Over the past half a century, significant efforts have been made to understand the regulatory mechanisms of sleep–wakefulness; however, there are several questions that remain unresolved. For example, why and how REM sleep appears only after several epochs of NREM sleep? How does the transition of vigilant states occur? How does the neural circuitry responsible for one specific vigilant state gets re-energized to induce the other vigilant state? Why is REM sleep present only in birds and mammals? Does sleep exhibit universal evolutionary and functional traits across phylogeny? Are the brain and body differentially susceptible to sleep loss? Answers to these questions await future studies.

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Sleep: Findings in Invertebrates and Lower Vertebrates

2

Abstract

Sleep is almost universally present throughout the animal kingdom, yet how sleep has evolved is not known. From an evolutionary aspect, a majority of animals that have been studied so far exhibit sleep or sleep-like states. Studies on sleep in different species belonging to vertebrate and invertebrate categories have provided novel insights into the evolution of sleep. The presence of a sleep-like state in jellyfish, a simple diploblastic animal having a noncephalized brain and no centralized nervous system, suggests that sleep/sleep-like state might have evolved even before brain cephalization occurred. The sleep-like state has been reported through observational studies in several species such as coelenterates, nematodes (roundworm), annelids, arthropods and mollusks, fishes, amphibians, reptiles, birds, and mammals. Electrophysiological correlates have also been recorded in a few species. The changes in low-frequency waves and spike-like activity in the EEG during the sleep-like state have been reported in crayfish, *Drosophila*, octopuses, some frogs, green iguanas, and box turtles. The activity of some EEG electrical waves changes from active to sleep-like state in all these organisms. This electrical activity could be the electrophysiological signature of the sleep-like state in nonmammalian and nonavian species. It is possible that such electrophysiological correlates evolved phylogenetically in mammalian and avian sleep. In this chapter, we have attempted to provide a comprehensive overview of the current knowledge about the evolution and presence of a standard signature of sleep across different species.

Keywords

Activity · Rest phase · Sleep-like state · Sleep evolution · Sleep posture · Quiescence state

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2.1 Introduction

Similar to any other biological process, sleep also shows evidence of phylogenetic evolution. However, it does not show any fossilized proofs. We can only understand the evolutionary signature of sleep through its manifestations and general nature in surviving forms. Sleep or rest phase has been found in every species as it is widespread across invertebrates and vertebrates. In invertebrates, the sleep-like state has been observed in some species of coelenterates, nematodes (roundworm), annelids, arthropods, and mollusks. In the vertebrates, however, sleep and the sleep-like state have been comprehensively studied in several species of fishes, amphibians, reptiles, birds, and mammals. A few pieces of evidence indicate that sleep/sleep-like state must have evolved along with the development of the centralized nervous system and brain cephalization. Nevertheless, studies also support the view that the sleep-like state may be present universally in all organisms irrespective of brain cephalization and/or development of the centralized nervous system.

Cnidarians (coelenterates) have simple nervous systems, whereas nematodes, annelids, arthropods, and mollusks have developed a centralized nervous system with brain cephalization. In terms of cellular complexity, cnidarians (jellyfish) show the presence of differentiated cell types in each tissue layer, such as nerve cells (including motor and sensory neurons), which are part of a primitive nervous system (Grimmelikhuijzen and Westfall 1995). A centralized nervous system and cephalization evolved first in Platyhelminthes (flatworm), which became evolutionarily developed further in nematodes, annelids, arthropods, and mollusks (Sarnat and Netsky 2002). Surprisingly, the echinoderms lost the centralized nervous system and brain during evolution (Cobb 1995). The nervous system of all nematodes (roundworm) consists of a central nervous system (CNS) with a "circumoral ganglionic brain" or "nerve ring" and a nerve cord running longitudinally from the head to tail region (Sarnat and Netsky 2002; Schafer 2016). Annelids also have the CNS with a prostomial brain and a ventral nerve cord (Beckers et al. 2019). The CNS of arthropods consists of a dorsal cephalic ganglion, the "brain", followed by a chain of ventral ganglia, the ventral cord. The brain of an arthropod consists of three pairs of ganglia: the protocerebrum (innervates to the eyes), the deutocerebrum (innervates to the antennae and plays a role in chemo and tactile sensation), and the tritocerebrum (integrates sensory information from protocerebrum and deutocerebrum) (Smarandache-Wellmann 2016). The nervous system of mollusks has a central and peripheral nervous system. The central part includes the brain proper and the optic lobes, while the large peripheral part includes the nervous system of the body and of the arms (Budelmann 1995). Sleep/sleep-like state has been investigated in cnidarians, nematodes, arthropods, and mollusks, but it has not been investigated in any of the annelids and echinoderms. Cnidarians do not have a centralized nervous system, but they demonstrate a cyclical and reversible sleep-like state. It is likely, therefore, that the sleep-like state may be present universally in all organisms irrespective of brain cephalization and/or development of a centralized

nervous system. As we go along this review, we will see that a common evolutionary signature of the sleep-like state is present across different phyla.

2.2 Sleep/Rest in the Invertebrates

2.2.1 Coelenterates: A Reversible Quiescent State in Jellyfish Is a Sleep-Like State

The studies on jellyfish suggest that it may have a reversible quiescent state similar to a sleep-like state. *Cassiopea* jellyfish are a rare swimmer and mostly remain immobile in an inverted posture (Fig. 2.1). *Cassiopea* exhibits a reversible quiescent state with subdued responsiveness to the external stimuli. A continuous bell pulsation is a hallmark of *Cassiopea*'s activity, which helps in generating fluid currents for filter-feeding and circulation and expulsion of metabolites and byproducts within and outside of the body. The bell of *Cassiopea* pulsates at a rate of about 1 pulse/s, but surprisingly, it has been observed that the pulsation rate varies across day and night (Nath et al. 2017). Nath et al. (2017) have reported that *Cassiopea* showed an average pulse activity of 1155 $\pm$ 315 pulses/20 min during daytime, which significantly decreased to 781 $\pm$ 199 pulses/20 min at night. The inter-pulse interval was longer, and responsiveness to the stimulus was reduced during the night compared to the daytime.

Furthermore, the quiescent state in the night in *Cassiopea* was found to be homeostatically regulated. Animals were quiescent-state deprived for 6 h, and it

Fig. 2.1 Upside-down jellyfish (*Cassiopea andromeda*). Attribution: Bjoertvedt / CC BY-SA (https://creativecommons.org/licenses/by-sa/4.0), File URL: https://uptoad.wikimedia.org/wikipedia/commons/2/2a/Cassiopeia_xamachana_upsidedown_jellyfish_LoroParque_IMG_5405.JPG. This file is licensed under the Creative Commons Attribution-Share Alike 4.0 International, which permits unrestricted me, distribution, and reproduction in any medium, provided the original author and source are credited

was found that *Cassiopea* exhibited a significant decrease in activity during the first four recovery hours. It was consistent with an increased sleep-drive after sleep deprivation in mammals.

Similar marked diurnal behavior has also been observed in the box jellyfish. The box jellyfish remains very active during the daytime; however, during the periods of inactivity at night, the jellyfish lie motionless on the seafloor, with entirely relaxed tentacles and no bell pulsation (Seymour et al. 2004). The jellyfish does not have a central nervous system, although it has a few elementary sets of neurons, which are involved in the detection of limited sensory stimuli such as touch, temperature, and salinity. Therefore, it remains an intriguing question how jellyfish regulate their quiescent and active states. Nevertheless, the sleep-like quiescent state in jellyfish indicates that such a state must have evolved much before the evolution of a well-organized central nervous system.

2.2.2 Nematodes: A Quiescent Behavioral Stage in the Nematode (Roundworm) Is Also a Sleep-Like State

The quiescent behavioral stage in the nematode [*Caenorhabditis elegans* (*C. elegans*)] is a sleep-like state (Fig. 2.2). In the aquatic environment, *C. elegans* actively swims, alternating between the continuous swimming and episodic

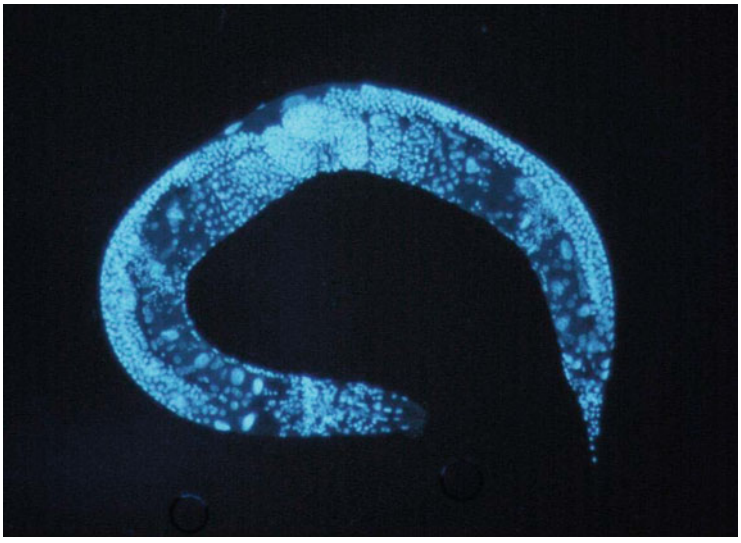

Fig. 2.2 *Caenorhabditis elegans* (*C. elegans*). This image is a work of the National Institutes of Health, part of the United States Department of Health and Human Services. As a work of the U.S. federal government, the image is in the public domain. The use of this figure does not require permission. https://ticket.wikimedia.org/otrs/index.pl?Action=AgentTicketZoom&TicketNumber=2007021510020148

swimming periods (Ghosh and Emmons 2008). During episodic swimming, *C. elegans* exhibits a phase of regular active swimming followed by a quiescent state. A set of neurons, including the command interneurons, is involved in switching these behavioral patterns.

Furthermore, it has been found that the motor circuits spontaneously switch from active to inactive behavioral states (Ghosh and Emmons 2008). The signaling of an acetylcholine neurotransmitter not only modulates transition from the swimming to quiescence state but also promotes the quiescence state and inhibits the active phase of swimming (Ghosh and Emmons 2008). Moreover, the body posture and the awakening ability from the quiescent state after poking were found to be similar to the other quiescence states, such as during lethargus or epidermal growth factor-induced quiescence (Ghosh and Emmons 2008). Therefore, it has been proposed that the quiescent behavioral stage of *C. elegans* could be a sleep-like state.

In addition to the quiescence state, the lethargus stage of *C. elegans* also shares some similarities with the sleep-like state. The life cycle of *C. elegans* comprises (a) the embryonic stage, (b) four larval stages (L1–L4), and (c) adulthood (Frand et al. 2005). The end of each larval stage is marked with a molt where a new stage-specific cuticle is synthesized, and the old one is shed (Cassada and Russell 1975). The larvae become inactive between the transition phase for a brief period, and it is known as the lethargus stage. This stage coincides with the separation of the old exoskeleton from the epidermis. In *C. elegans*, molting requires the expression of several proteins. For example, the low-density lipoprotein receptor-like protein "LRP-1", a sterol-modifying enzyme LET-767, nuclear hormone receptors [(NHRs), NHR-23 and NHR-25], and the ecdysone receptor components EcR and USP (ultraspiracle) play an important role in molting in *C. elegans* (Frand et al. 2005). Raizen et al. have reported that the quiescence associated with lethargus has sleep-like properties, that is, reversibility, reduced responsiveness, and homeostasis (Raizen et al. 2008). Additionally, they have identified a cGMP-dependent protein kinase (PKG) gene "egl-4", which promotes the sleep-like state in *C. elegans* (Raizen et al. 2008). Molting is very important for growth and development and is present in diverse groups of animals (Frand et al. 2005). Several biosynthetic activities required for molting occur during the quiescent state. It has been noted that the behavioral quiescence stage in *C. elegans* appears after satiety, intense episodic swimming, and also at a specific time (Ghosh and Emmons 2008; Raizen et al. 2008; You et al. 2008). The lethargus stage is accompanied by bouts of quiescence as well as motion (Iwanir et al. 2013). Importantly, the animals maintain a characteristic body posture during lethargus (Iwanir et al. 2013). These findings suggest that quiescence during the lethargus period has similarities with the sleep-like state.

2.2.3 Annelids: Do Leech and Earthworm Exhibit Sleep-Like State?

Whether the quiescence or lethargic states in annelids have any similarity with the sleep-like state is not known. It has, however, been observed that certain leeches

Fig. 2.3 Predatory leech (*Hirudinea*). Taken from https://pixabay.com/photos/leech-medical-leech-angler-bait-368345/ and modified. Pixabay License Free for commercial use

(Fig. 2.3) typically remained inactive or went into hiding under the stone during the day, but their activity increased dramatically at night (Angstadt and Moore 1997; Morrison 2013). If these daily active–inactive phases of annelids have any similarity with the sleep-like state requires an in-depth study. Interestingly, the serotoninergic system modulates the daily activity patterns of annelids (Burns et al. 1991). Burns et al., have reported that the locomotion rates in earthworms (Fig. 2.4) increased 6 h after injection of *p*-chlorophenylalanine (which decreased serotonin levels). On the other hand, 6 h after 5-hydroxy-L-tryptophan (5-HTP) injection (which increased serotonin level), the locomotion rate in the earthworms decreased (Burns et al. 1991). They have also reported that earthworms injected 6 h previously with 5-HTP crawled slowest at 24 h periods compared to the controls. When the locomotion rate was determined among the four times of day, the responses to 5-HTP were not uniform; instead, it exhibited a circadian rhythm (Burns et al. 1991). It is not known if serotonin influences the sleep-like state in annelids. However, serotonergic neurons induce a sleep-like state in *C. elegans* and *Drosophila* (Trojanowski et al. 2015; Yuan et al. 2006). It is also remarkable that earthworms exhibit a coiled posture during the facultative diapause or quiescence period (Darío et al. 2006). These findings indicate that annelids may also be experiencing some sleep-like states.

Fig. 2.4 Earthworm (*Lumbricus*). Taken from https://pixabay.com/photos/the-worm-earthworm-polychactcs-3555821/ Pixabay license Free for commercial use

2.2.4 Arthropods: High-Amplitude Slow Waves Appear During Putative Sleep in the Crayfish

Besides the behavioral paradigms, the changes in electrophysiological correlates during the activity and sleep-like state were first characterized in the crayfish. Ramon et al. have shown for the first time that a behavioral sleep-like state in crayfish was accompanied by high-amplitude slow-wave electrical activity of the brain. It was quite distinguishable from a waking period.

Crayfish (*Procambarus clarkia*) (Fig. 2.5) is a crustacean that belongs to the phylum Arthropoda and possibly exhibits a resting state similar to the sleep-like state. As mentioned earlier, there are three main regions in the crustacean brain: the proto-, deuto- (or deutero), and tritocerebrum. Each region contains specialized areas of neuropil that are associated with particular sensory structures (Utting et al. 2000). Ramon et al. have reported that in the laboratory aquarium, the crayfish exhibits four general body positions during wakefulness and sleep-like state: (1) walking at the bottom of the aquarium, with chelae extended at the level of the rostrum, (2) standing up motionless on extended pereiopods, (3) standing up motionless on flexed pereiopods, with chelae flexed, tail curled, and antennae and antennulae low, and (4) lying on one side just under the surface of the water, with chelae extended. The last body position is viewed as the sleep/rest phase in the crayfish (Ramon et al. 2004).

Spontaneous brain electrical activity was recorded from the protocerebrum brain areas during wakefulness and sleep-like state in the crayfish (Ramon et al. 2004). Ramon et al. observed the monophasic or biphasic spikes of varying amplitude when the crayfish were walking around the aquarium or were motionless in an upright position (positions 1–3). The spikes, however, completely transformed into

Fig. 2.5 Crayfish (*Procambarus clarkia*). Taken from: https://pxhere.com/en/photo/766404; CC0 Public Domain Free for personal and commercial use

synchronous 8-Hz slow waves with relatively high amplitude during the sleep-like state, that is, when the crayfish were lying on one side (position 4) (Ramon et al. 2004). This slow-wave pattern changed into spikes again when the crayfish was perturbed or attained the standing-up position. The arousal threshold was also higher during this position (position 4). Such slow-wave activity had never been reported earlier in any invertebrate during the sleep-like state. Furthermore, the wavelet analysis and its correlation with body position revealed that the power of electrical waves in the frequency range 30–45 Hz decreased during the sleep-like state, and slow waves were generated 1–2 min after the animal lies on one side. The strong correlation between slow waves and lying on one side position shows that it could be characteristic of the sleep-like state in the crayfish (Mendoza-Angeles et al. 2007). The electrical activity has also been recorded from different brain areas in the crayfish, which demonstrated that the slow waves are present in the central area of the brain during the wake condition. However, slow waves spread first to deuto- and then to protocerebrum during sleep. It was proposed that the central brain area of the crayfish could be acting as a sleep generator (Mendoza-Angeles et al. 2010).

2.2.5 The Changes in Brain Electrical Waves During the Rest and Activity Phases in Fruit Fly (*Drosophila melanogaster*)

The sleep/rest phase in *Drosophila* (Fig. 2.6) shares two primary sleep characteristics: (a) increased arousal thresholds and (b) its homeostatic regulation. It has been observed that the sleep-like state in *Drosophila* is sensitive to prior amounts of waking activity, biological clock, pharmacological manipulation, and

Fig. 2.6 Fruit fly (*Drosophila melanogaster*). This figure is licensed under the Creative Commons Attribution 2.0 Generic license. Taken from: https://www.flickr.com/photos/52450054@N04/15675291741/ Author: Judy Gallagher

alterations in the specific gene expression (Cirelli and Bushey 2008). Also, electrophysiological correlates during the sleep-like state and activity phase have been recorded in *Drosophila* (Nitz et al. 2002). Unlike crayfish, Nitz et al. have observed that local field potential (LFP) spiking decreased during the sleep-like state compared to the activity phase. The LFP power across all frequency bands reduced during the sleep/rest phase compared with the active periods (Nitz et al. 2002). The LFP activity demonstrates a dynamic relationship with movements and arousal threshold (van Swinderen et al. 2004). It was proposed that the communication between movement and brain LFP activity might have decreased in the medial protocerebrum with time. Such communication uncoupling between movement and brain LFP activity plays a role in increasing arousal thresholds (van Swinderen et al. 2004). Therefore, it appears that such considerable changes in the brain's electrical activity could be closely linked to changes in behavioral states (Nitz et al. 2002; van Swinderen et al. 2004).

In *Drosophila*, the activity and sleep-like states are modulated by specific neural circuitries. The mushroom body in the *Drosophila* brain regulates active and sleep-like states. Complete ablation of mushroom bodies or their momentary inhibition by using temperature cycles reduces sleep-like states (Joiner et al. 2006). LFP recordings between the mushroom bodies and the lamina or medulla of the optic lobes were consistently accompanied by spike-like potentials during the active phase and tended to occur in bursts. In contrast, the spikes were significantly less in number when the recording was obtained from bilateral optic lobes (Nitz et al. 2002). Such findings suggest that the sleep-like state in *Drosophila* indeed exhibits changes in brain electrical activity. However, contrary to the recording of brain activity in crayfish, the sleep-like state in *Drosophila* is associated with a decreased incidence of spike-like LFP activity.

Serotonin plays an important role in the regulation of the sleep-like state in *Drosophila*. The mutant flies of the d5-HT1A receptor exhibited short and fragmented sleep (Yuan et al. 2006). The fragmented sleep in such mutant flies was rescued by expressing the d5-HT1A receptor in the mushroom bodies. The mutant flies of d5-HT2 or d5-HT1B receptors exhibited normal sleep-like patterns, suggesting that serotonin modulates sleep through d5-HT1A receptors in the mushroom bodies. Further enhancing serotonin levels either through pharmacological or genetic intervention enhanced sleep in wild-type flies. Also, serotonin plays a role in sleep compensation in short sleeper flies. Similar to mammalian aminergic system of arousal, dopamine and octopamine are arousal-inducing neurotransmitters in *Drosophila* (Andretic et al. 2005; Crocker et al. 2010). The arousal and sleep-associated neuronal circuitries have been identified in detail in *Drosophila*, which is why *Drosophila* is widely used as one of the favored model organisms in sleep research.

2.2.6 Mollusks: Sleep-Like States with Rapid Eye Movements and Twitching in the Cuttlefish (*Sepia officinalis*)

The cuttlefish (*Sepia officinalis*) (Fig. 2.7), a mollusk, exhibits two distinct sleep-like states. Frank et al. have reported that adult and juvenile *Sepia* exhibited some of the sleep-associated behavioral criteria such as stereotyped posture, inactivity, and homeostatic regulation. Interestingly, one additional sleep-like state with twitching of arms, eye movements, and nonrandom chromatophore activity has also been observed by their group (Frank et al. 2012). They noted that out of three key criteria of sleep (an increased arousal threshold, a rapid reversal to an alert state, and rebound sleep), the cuttlefish exhibited only some of the criteria during the sleep-like state

Fig. 2.7 Cuttlefish (*Sepia officinalis*). Taken from: https://www.flickr.com/photos/briangratwicke/10338154375 Author: Brian Gratwicke

(Frank et al. 2012). Cuttlefish exhibited a sleep-like quiescent period with spontaneous bursts of arm and eye movements, which accompanied with rapid changes in the skin chromatophore patterns. The quiescent periods appeared cyclically, and the mean episode duration length was approximately 2.42 min (Iglesias et al. 2019). Iglesias et al. have also reported that the sleep-like state with twitches occurs in adults as well as younger animals, and the expression of the sleep-like state follows an ultradian pattern (Frank et al. 2012; Iglesias et al. 2019). Frank et al. and Iglesias et al. have also observed that cuttlefish exhibited intermittent dynamic "chromatophore body patterning" during the jerky-sleep-like state. The cuttlefish displays specific body patterns in response to stimuli, such as the appearance of predators, prey, and during courtship through the chromatophore system (Tublitz et al. 2006). Expression of aggression, predatory-like attacks, and sleep-related erections during REM sleep have also been found in mammals, including humans (Schmidt and Schmidt 2004; Zagrodzka et al. 1998). It is an exciting observation that cuttlefish displays a body pattern during the jerky-sleep-like state, which could be similar to the behavior observed in mammals. Mollusks, in comparison, possess a developed brain and exhibit complex behavior. Hence, the presence of REM sleep-like state even with some minimal features actually demonstrates the evolutionary aspect of sleep and its nature.

2.2.7 Sleep-Like State with a Closed Eye and Random Movements of the Arm's Suckers in *Octopus vulgaris*

Both behavioral and brain electrophysiological correlates have demonstrated a sleep-like state in *Octopus vulgaris* (Brown et al. 2006; Meisel et al. 2011). *Octopus vulgaris* (Fig. 2.8) exhibits rest periods, which has been characterized by a time-of-day effect, decreased responsiveness to external stimuli, rest rebound after deprivation, and some changes in the brain electrical activity (Brown et al. 2006; Meisel et al. 2011). Meisel et al. have reported that the activity cycles followed circadian timing, and the arousal threshold was more during the quiescent periods. In their detailed behavioral observations, they found that octopuses demonstrated a preferred resting place, actively built a den site, and a prototype posture of quiescence. Similar to the jerky-sleep-like state in the cuttlefish, the octopuses also demonstrated a jerky-quiescence period with random movements of the suckers on the arms (Meisel et al. 2011).

Interestingly, the rebound of the sleep-like state occurred when animals were deprived of this state during the night, but such a rebound did not occur when they were deprived during the daytime (Meisel et al. 2011). Octopuses also showed a typical "half-and-half" skin pattern during the periods of rest, which was not camouflage matched to the environment (Meisel et al. 2011). Meisel et al. have defined the quiescence stage as sleep in the octopus because it shared a few similarities with mammalian sleep. For example, octopuses exhibited peculiar sleeping postures during which the pupil of eyes was narrow or eyes were completely closed. The body was motionless, but at times, they noticed that there was a

Fig. 2.8 *Octopus vulgaris.* Attribution: Albert Kok at Dutch Wikipedia (Original text: Albert Kok) / Public domain. File URL: https://upload.wikimedia.org/wikipedia/commons/9/9f/Octopus_vulgaris_2.jpg

rapid-jerky movement of the suckers, the head was down, and the arms were curled around the body. They have also noticed that the ventilation rate substantially reduced during the sleep-like state (Meisel et al. 2011). Brown et al. have found that the vertical lobe of the brain in the octopus exhibited increased electrical activity during the behavioral rest, although only for short periods. They have proposed that similar to mammalian brain activity, the octopus also demonstrates a sleep-like state with a "body-off /brain-on" condition. In addition, they have proposed that similar to mammal's neural activity, the brain areas involved in memory or "higher" processes exhibit "off-line" activity during the sleep-like state in octopuses as well. These findings suggest that behavioral and electrophysiological correlates of the sleep-like state of the octopus are similar to the mammalian sleep. The sleep-like state in the octopuses also demonstrates the evolutionary signatures of sleep.

2.3 Sleep/Rest in Vertebrates

2.3.1 Fishes: Predominance of Power in the Low-Frequency Bands During Waking

Based on the similarities in the organization of the central nervous system with mammals, studies have been conducted to characterize sleep in fishes. Although behavioral sleep has been observed in fishes, electrophysiological correlates similar to mammals have not been observed reliably. Several studies have shown general

Fig. 2.9 *Zebrafish*. Taken from: Oregon State University / CC BY-SA (https://creativecommons.org/licenses/by-sa/2.0); File URL: https://upload.wikimedia.org/wikipedia/commons/6/6b/Zebrafish_%2826436913602%29.jpg (Modification: The picture of a single fish was taken)

behavioral, physiological, and pharmacological characteristics of sleep in the fishes (Hartse 1989). The lower animals will have obvious anatomical limitations in expressing the slow-wave patterns similar to mammalian sleep because these animals have a rudimentary neocortex, which may be unable to produce mammalian-like brain activity (Hartse 1989). However, the major neuronal architecture and neurotransmitters associated with sleep–wakefulness in mammals also seem to be conserved in fishes and help regulate the sleep/rest and alert behavior (Prober et al. 2006). Fishes show increased arousal threshold during the sleep-like state (Yokogawa et al. 2007), and as in mammals, the wakefulness-inducing neurotransmitter, orexin, is released by the neurons of the posterior hypothalamus (Yokogawa et al. 2007). Such findings advocate the archaic organization of the circuitry associated with the regulation of sleep/rest behavior in the fishes.

In zebrafish (Fig. 2.9), a continuous period of inactivity of atleast 1 min is characterized as the sleep/rest phase. The total sleep for each day and night periods is computed and is plotted as an average sleep/10 min to generate a sleep time course. Sleep bout number and length are defined as a continuous period of inactivity lasting 1 min or longer. The sleep latency parameter was also computed, which was defined as the amount of time from the start of each day and night period until the first sleep bout. Furthermore, by measuring the average activity during bouts of waking, one can assess the overall health and swimming ability of the fish. Average activity per waking minute was calculated for each day and night period by summing the total activity and dividing by the number of active minutes (total active minutes = total time − total sleep time) (Rihel et al. 2010). The brain wave recording across different vigilant states in fish has been performed, but no differences in cerebral activity between states have been observed. Spectral analysis of short EEG fragments revealed a predominance of power in the low-frequency bands during waking (Campbell and Tobler 1984).

The inherent behavior regarding the expression of increased or decreased sleep (amount or duration) could be because of different genetic imprinting. Recently, it

has been shown that certain transgenic fish exhibited increased sleep amount, while other genetic variants had decreased sleep amount (Zada et al. 2019). Yokogawa et al. have generated a mutant zebrafish with a disrupted hypocretin system. Surprisingly, the mutant fish did not exhibit sleepiness or paralysis; total sleep time, however, was reduced by 30% at night (Yokogawa et al. 2007). They had further investigated the relationships between the hypocretin system and other sleep regulatory brain systems and observed differential expression patterns in the brain. Studies on zebrafish now indicate that how the sleep regulatory system may have evolved across vertebrate phylogeny (Chiu and Prober 2013; Yokogawa et al. 2007). Therefore, the zebrafish is being widely used as a model to study sleep and arousal states. It is becoming popular day by day and may provide new insights into genetic and neural mechanisms of sleep–wakefulness.

2.3.2 Amphibians: EEG Bursts During the Sleep-Like State in Frogs

Behavioral evidence shows that amphibians also exhibit a rhythmic and cyclical rest phase during which heart and respiratory rate slow down. Karmanova has reported that some of the frogs spent 80–90% of a 24-h period in the resting state (Karmanova 1982). Some of the amphibian animals, such as the western toad (*Anaxyrus boreas*) (Fig. 2.10a), have exhibited increased arousal threshold from the rest phase, while no such response was found in the American bullfrog (*Lithobates catesbeianus*) (Fig. 2.10b) (Allan Hobson 1967). Hobson reported that the undisturbed frogs had maintained the resting postures for long hours. Bullfrog even did not show any change in the threshold of respiratory responses to cutaneous shock during the rest to activity cycle or vice versa. Most importantly, the pattern of EEG in the rest phase was just opposite to the pattern of the avian and mammalian sleep. The EEG changed to a low-voltage high-frequency pattern in the rest condition and high-voltage

Fig. 2.10 (**a**) Western toad (*Anaxyrus boreas*). Attribution: https://www.flickr.com/photos/oregonstateuniversity/6151328558/in.photostream/; Author: Oregonstate University, (**b**) American bullfrog (*Lithobates catesbeianus*). Attribution: Carl D. Howe / CC BY-SA (https://creativecommons.org/licenses/by-sa/2.5), File URL: https://upload.wikimedia.org/wikipedia/commons/a/aa/North-American-bullfrog1.jpg, and (**c**) music frog (*Babina daunchina*). Taken from: Gang Wei et al. Zookeys 904: 60–87 (2020) doi: 10.3897/zookey.904.39161. This is an open access article distributed under the terms of the Creative Commons Attribution License (CC BY 4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited

slow-frequency pattern in the active phase. Hobson once doubted if sleep was at all present in the American bullfrog (Allan Hobson 1967).

Afterward, using both behavioral and neurophysiological characteristics, three forms of sleep-like states were determined in frogs (Kulikov et al. 1994). Although the brain's electrical activity during wakefulness and sleep-like state exhibited only marginal alterations, the muscle tone drastically changed during different vigilant states. Therefore, it was used as a primary criterion to determine the sleep-like state in frogs (Lazarev 1978). Three different sleep-like states characterized were (1) sleep-like state with a plastic muscle tone of "cataleptic" type, (2) rigid muscle tone of "catatonic" type, and (3) relaxed tone of skeletal musculature as "cataplexy" state (Kulikov et al. 1994). Changes in electrophysiological correlates of the amphibian brain activity across these three behavioral sleep-like states, however, did not confirm these stages. Based on the peculiar muscle activity during such sleep-like states, it was considered as "protosleep" or primary sleep (Aristakesyan 2016). During the sleep-like state, spike-like activity in the EEG had an amplitude of 40–50 μV in the frequency range 10–50 Hz, which disappeared along with spontaneous or induced awakening (Kulikov et al. 1994). Also, the amplitude of brain electrical waves increased from the sleep-like state to the active phase (Hartse 1989). Since the spike activity in the EEG increases with the deepening of the quiescence state, it was proposed as a characteristic of the amphibian sleep-like state (Hartse 1989; Lazarev 1978).

Fang et al. (2012) have found functionally relevant frequency bands in the EEG across the vigilant state in music frogs (*Babina daunchina)* (Fig. 2.10c) (Fang et al. 2012). They observed that EEG power was concentrated in four frequency bands during the active state and three frequency bands during the rest state. The prevalent four frequency bands during wakefulness were 1–4 Hz delta band, 6–8 Hz theta band (14 Hz waves covaried with theta band), 9–17 Hz alpha band (5 Hz and 20–21 Hz waves covaried with the alpha band), and 16–45 Hz beta band. They could not identify gamma bands during the waking state. The observed prevalent waves in three different frequency bands during the sleep-like state were 1–5 Hz slow band (which covaried with frequencies from 9–10 to 15 Hz), 11–14 Hz intermediate band (which covaried with frequencies from 6–7, 16–17, to 19 Hz), and 17–45 Hz fast frequency band (which covaried with 6–8 Hz waves) (Fang et al. 2012). Although the power in EEG bands in frogs differed substantially from humans and rats, the EEG bursts in the resting frogs were similar to mammalian NREM sleep spindles. It was, hence, proposed that sleep spindle-like EEG activity might have appeared before the evolution of mammals (Fang et al. 2012).

2.3.3 Reptiles: Spike and Sharp-Wave Activity During Behavioral Sleep

Similar to fishes and amphibians, reptiles also exhibit a different sleep pattern from the mammalian and avian sleep (Gonzalez et al. 1999). Nevertheless, the type of behavior that is usually classified as sleep in mammals and birds is also present

Fig. 2.11 Box turtle (*Terrapene carolina*). Attribution: I, Jonathan Zander / CC BY-SA (http://creativecommons.org/licenses/by-sa/3.0/). File URL: https://upload.wikimedia.org/wikipedia/commons/3/34/Florida_Box_Turtle_Digon3.jpg

Fig. 2.12 Green iguana (*Iguana iguana*). Attribution: Normantas / CC BY-SA (https://creativecommons.org/licences/by-sa/4.0) File URL: https://upload.wikimedia.org./wikipedia/commons/b/bf/Green_Iguana_Florida.jpg

consistently in reptiles (Hartse 1989). For example, lizards remain immobile and keep their body musculature relaxed maximally during the sleep-like state. Also, the respiratory and cardiac activity decreases, and behavioral responsiveness to arousal stimulus turns substantially low (Flanigan 1973).

Flanigan et al. (1974) have studied behavioral as well as electrophysiological correlates during activity and the sleep-like state in box turtles (*Terrapene carolina*) (Fig. 2.11). The electrodes were chronically implanted in the forebrain, midbrain, and orbital cavities in extraocular and nuchal muscles and the dorsal shell in box turtles. Behaviorally, they observed that the box turtle exhibited four different postures during different vigilant states. (a) Stage 1: during the active wake, the limbs and neck were extended with the head elevated, and eyes were open; (b) stage 2: during the quiet wake, the posture was similar to active wake, but the shell was resting on the floor. During sleep-like states, animals showed two different stages: (c) stage 3: animals exhibited slightly flexed limbs, or one-three limbs were extended backward parallel to the body, the neck was extended, and the head was resting on the floor with closed eyes; and (d) stage 4: all limbs were extended backward and the head was resting on the floor with eyes closed (Flanigan et al. 1974). They reported that EEGs were marginally lower in frequencies and amplitudes during behavioral sleep. Neither epochs of slow waves nor paradoxical sleep was recorded, although spike and sharp-wave activity were at peak during behavioral sleep (Flanigan et al. 1974).

Similarly, the green iguana (*Iguana iguana*) (Fig. 2.12) exhibited four different vigilant states: (a) active wakefulness, (b) quiet wakefulness, (c) quiet sleep, and (d) active sleep (Ayala-Guerrero and Mexicano 2008). The amplitude and frequency of cortical brain activity decreased from wakefulness to quiet sleep. However, both parameters increased slightly during active sleep. The tonic and phasic muscular activity were present during wakefulness, which decreased or disappeared in quiet sleep, but surprisingly reappeared during active sleep. Eye movement (single or conjugate) was also observed during wakefulness, which disappeared in quiet sleep, but reappeared during active sleep (Ayala-Guerrero and Mexicano 2008).

In reptiles, the amplitude and frequency of EEG, amplitude of EMG, and heart rate decrease during the sleep-like state compared to wakefulness (Flanigan 1973; Hartse 1989). The sleep-like state in reptiles is, however, accompanied by arrhythmic and intermittent high-voltage spikes, which disappear during spontaneous or forced wakefulness (Flanigan 1973; Hartse 1989). The energy in the EEG spectral power remains high in the low-frequency band during alertness, as characterized by opened eyes (Gonzalez et al. 1999). Also, the power decreases significantly in both high- and low-frequency bands during the night, which is the rest phase in lizards (Gonzalez et al. 1999). Contrary to this, the EEG spectral band in the low-frequency range remains high during NREM sleep in mammals and birds (Jha et al. 2006). This suggests that there are some qualitative similarities in the EEG power in the low-frequency range between lizards and mammals but in opposite vigilant states. This led Gonzalez et al. to reason that reptilian waking could have evolved into mammalian slow-wave sleep (Gonzalez et al. 1999). Although reptilian and mammalian sleep shares many behavioral similarities, their brain electrical activity does not correlate with each other, raising doubts on the mammalian and avian sleep evolution sharing its link with their common forerunner, the reptiles.

2.4 Conclusion

In summary, studies demonstrate that a sleep-like state is universally present in all organisms across different phyla. Evidence does not support the concept that it might have evolved along with the development of brain cephalization. It is also present in organisms, such as jellyfish, which do not have a cephalized brain or a centralized nervous system. Although the study of the sleep-like state in starfish (which also does not have a cephalized brain) is lacking, such a study may provide some conclusive evidence for the evolution of the sleep-like state in the noncephalized brain. Also, it looks apparent that the behavioral signature of the sleep-like state across different organisms is universal. The electrophysiological signature, however, may not be common in all organisms, but some animals such as crayfish, green iguanas, and box turtles exhibit peaks of slow-wave, spike, and sharp-wave activity during the sleep-like state. It is possible that such electrophysiological correlates evolved phylogenetically in mammalian and avian sleep.

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Sleep: Evolutionary and Adaptive Changes in Birds and Mammals

3

Abstract

Several pieces of evidence suggest that sleep exhibits progressive phylogenetic development as well as inter- and intraspecies variation. Birds and mammals show a complex dual nature of sleep characterized as NREM and REM sleep. At the same time, aquatic mammals do not have REM sleep. The semiaquatic mammals exhibit REM sleep when they sleep on land but do not show REM sleep when they sleep in water. Interestingly, some birds and aquatic mammals also exhibit a unique sleep; that is, one side of the brain sleeps, and the other half of the brain remains awake. Such evolutionary changes in sleep are best suited for their survival as they can perform some difficult tasks while asleep. Furthermore, sleep gets significantly compromised under certain situations, such as during pregnancy and postpartum periods. We do not know yet if the compromise of sleep could be the demand of the situation and if it bears some cost on our health, or is it that nature helps in reappropriating the sleep demand. Sleep alteration at the micro- and macrolevels is common with normative aging, and certain changes are clearly linked with the pathophysiology conditions. In this chapter, we discuss the sleeping patterns, sleep strategies, and sleep consolidations across phylogeny and aging. It is essential for us to understand the current challenges in our society, where we experience poor sleep quality and insufficient sleep and we wake up tired almost every day. The sleepless society cannot be healthy and productive, and sleep disruption may cost our reproductive efficiency and, ultimately, our survival. It is, therefore, essential to learn from birds and aquatic mammals how to develop skills and strategies for sleep management.

Keywords

Aging · Aquatic adaptation · Bihemispheric sleep · Migration · Pregnancy · Unihemispheric sleep

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3.1 Introduction

Similar to other biological processes, sleep also exhibits progressive phylogenetic development. Phylogenetically, birds and mammals show two distinct sleep stages: (a) non-rapid eye movement or slow-wave sleep (NREM or SWS) and (b) rapid eye movement (REM) sleep (Jha et al. 2006; Zepelin et al. 2005). NREM sleep in most mammals exhibits cyclic progression to different substages such as N1, N2, and N3 in humans and SWS-I and II in the cat, dog, and other mammals (Berry et al. 2012; Jha et al. 2006). Sleep in other vertebrates, such as fishes, amphibians, and reptiles, is unitary in nature (see Chap. 2). Also, some studies indicate that NREM sleep/SWS in birds is as evolved as in mammals; however, compared to mammals, REM sleep is less evolved in birds (Jouvet 1965). The NREM sleep and REM sleep with their associated changes in cortical activation are found only in mammals and birds, and it further demonstrates a striking similarity in avian and mammalian sleep (Lesku et al. 2008; Rattenborg and Martinez-Gonzalez 2015; Roth et al. 2006; Tobler 2005).

The nonmammalian and nonavian animals (invertebrates and lower vertebrates) exhibit a simple resting posture. Nevertheless, the majority of mammals and birds have developed a complex sleeping posture, which they frequently change possibly to attain utmost body rest (Fig. 3.1). For example, birds usually bury their bill into the scapular feathers or hide under the wing when asleep (Hill et al. 1980). The ground-foraging birds such as pheasants perch on the ground or in the low branches of trees and simply huddle up and tuck in their appendages. A report suggests that an extinct dinosaur "Mei long," a troodontid, had avian-like sleeping posture (Xu and Norell 2004). The fossil found of this creature demonstrates the stereotypical sleeping or resting posture, that is, "head tucked-in sleeping posture," which is invariably found in the existing birds. Why birds sleep in tuck-in posture is not clearly known, but such posture may help birds to reduce their surface area for heat conservation (Ferretti et al. 2019; Hill et al. 1980). Similarly, mammals such as lion, tiger, dog, and elephant sleep with their eyes closed and lie down on the ground, while the ruminants such as cow, sheep, and goat rest on the ground with their head bend towards the body (Fig. 3.1) (Zepelin et al. 2005). The giraffe sleep recumbently on the ground with the head resting on the hindquarters or ground and holding the neck in an arced posture (Zepelin et al. 2005). Aquatic mammals such as gray seals, northern fur seals, and walruses sleep while floating in the water (Zepelin et al. 2005). The whale sleeps in water in a vertical hanging posture (Miller et al. 2008). These suggest that, like any other evolutionary change in physiological phenotypes, sleep also shows the signature of phylogenetic evolution. Although avian and mammalian sleep demonstrates several similarities, there are yet some intriguing questions. Is avian and mammalian sleep fundamentally the same? Has NREM sleep converged closely across birds and mammals but not REM sleep? Why birds exhibit less amount of REM sleep compared to mammals? We have attempted to review in this chapter how close avian and mammalian sleep is, in terms of characters and functions.

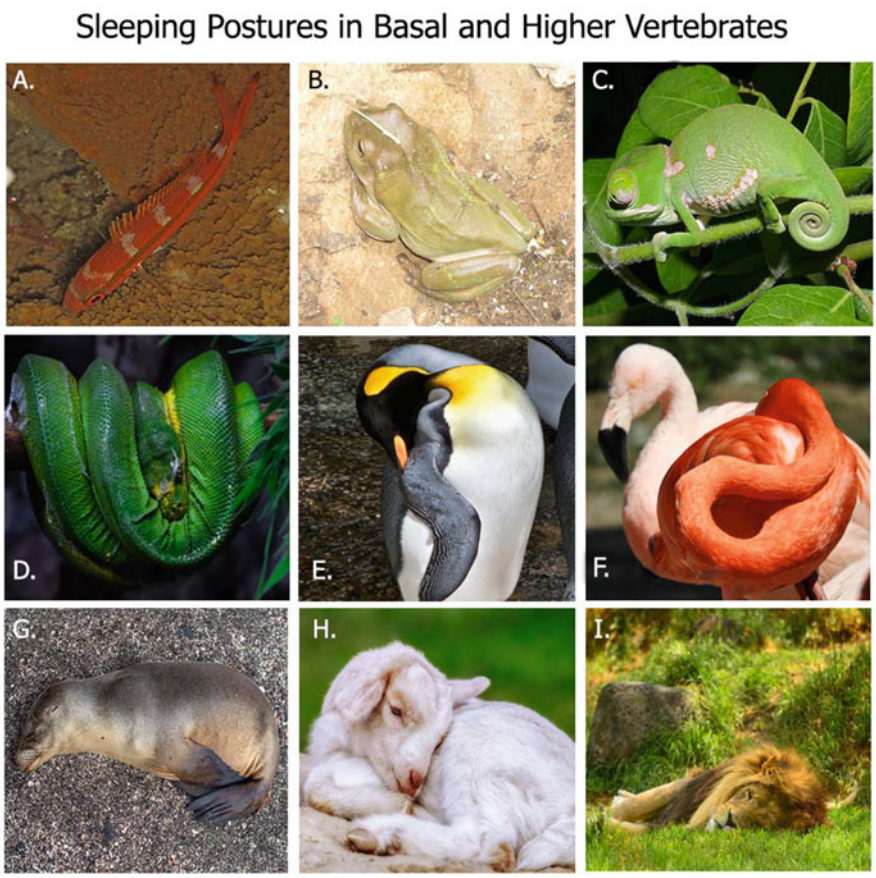

Fig. 3.1 The basal and higher vertebrates and their sleeping posture. It is difficult to determine from the sleeping postures of the basal vertebrates such as (**a**) fish, (**b**) frog, (**c**) chameleon, and (**d**) green snake, if they were quiet or asleep. However, birds (**e**) penguin and (**f**) flamingo and mammals (**g**) sea lion, (**h**) goat, and (**i**) lion demonstrate the phenotype of sleep-associated posture, i.e., body curling and beak tuck-in. (except the lion). Attributions: (**a**) Photo by: Lakshmi Sawitri / CC BY (https://creativecommons.Org/licenses/by/2.0). (**b**) Photo by: Vmenkov / CC BY-SA (https://creativecommons.Org/licenses/by-sa/3.0). (**c**) Photo by: Bernard Dupont from FRANCE / CC BY-SA (https://creativecommons.Org/licenses/by-sa/2.0). (**d**) Photo by: Dimitris Vetsikas from Pixabay. (**e**) Image by PollyDot from Pixabay. (**f**): Laura Fa; https://www.pexels.com/photo/bird-flamingo-pink-sleepinq-2240916/. (**g**) Nicolas Völcker / Wiícimedia Commons ShareAlike 4.0 International (CC BY-SA 4.0). (**h**) Photo by Couleur from Pexels. (**i**) Lion Photo by Chris Phutully from Australia / CC BY (https://creativecommons.org/licenses/by/2.0)

3.2 Sleep in Birds

Birds have evolved from the stem reptiles and exhibit two distinct phases of sleep: NREM sleep and REM sleep (Low et al. 2008). Two distinct sleep stages are also present in mammals, who have a well-developed neocortex and thalamus (Rattenborg 2006b). Although birds have well-developed thalamus but are devoid of a neocortex (Rattenborg 2006b), they express two distinct sleep states. It suggests that the neocortex is not necessary for the development of two distinct states of sleep that are present in the birds and mammals. Brain electrical signals recorded as EEG in birds are high-frequency waves having low amplitude during wakefulness and REM sleep, while prominent slow-wave activity with high amplitude in the range of 1–4 Hz during NREM sleep (Jones et al. 2008). However, slow-wave activity has never been observed in the EEG of sleeping reptiles, suggesting that the neuroanatomical and neurophysiological traits necessary for the genesis of slow waves must have evolved independently in birds and mammals.

Whether sleep in birds is homeostatically regulated is not clearly known. Some studies have reported that as the sleep-deprived mammals show a compensatory increase, the avian sleep does not show the signs of a compensatory increase in slow-wave activity during NREM sleep after sleep deprivation (Jha et al. 2006; Tobler and Borbély 1988). Hence, avian SWS may not be homeostatically regulated, and it could have quite different functions from mammalian sleep. However, some later studies have reported that avian sleep is also homeostatically regulated (Jones et al. 2008; van Hasselt et al. 2019). Tobler and Borbély (1988) found in their study that NREM sleep and EEG slow-wave activity during NREM sleep did not change; REM sleep, however, significantly increased after 24 h of sleep deprivation (Tobler and Borbély 1988). Jones et al. (2008) found that neither NREM nor REM sleep amount increased during recovery sleep following 6 h of total sleep deprivation. However, peak slow-wave activity during NREM sleep significantly increased in recovery sleep for the first 2 h after sleep onset, suggesting that sleep in birds is homeostatically regulated (Jones et al. 2008). Recently, van Hasselt et al. (2019) reported that sleep deprivation in the European starling bird increased the NREM sleep EEG spectral power from 1.17 to 25 Hz frequency range during the recovery sleep. NREM sleep amount also increased significantly, but only on the next day. They, however, did not find compensatory changes in REM sleep. They concluded that birds display signs of only NREM sleep homeostasis and not REM sleep (van Hasselt et al. 2019). These studies do suggest that there are certain striking differences existing between avian and mammalian sleep.

3.2.1 Sleep in Ancient Evolutionary Birds: The "Ostrich" and "Elegant Crested Tinamou"

Mammals and birds share several common distinctive features of sleep, but some ancient mammals such as the platypus, echidna, and ferret have the highest amount of REM sleep as well as a different REM sleep state that has a combined component

of NREM and REM sleep (Jha et al. 2006; Siegel et al. 1996, 1999). The evolutionary theory suggests that REM sleep possibly has evolved independently in birds and mammals from the stem reptiles, and that is why sleep in both should share some common characteristics. But it is not yet clearly known if the palaeognaths ("ancient birds") or certain neognaths ("evolutionary modern birds") also exhibit the ancient REM sleep state having mixed components of NREM and REM sleep. In one study, the recording of brain activity during sleep in ostriches (the member of living palaeognath family) demonstrated that the amount of REM sleep was highest in the ostrich compared to any other birds (Lesku et al. 2011). Also, the forebrain activity during REM sleep in ostriches frequently flipped between slow-wave activity and REM sleep-like electrical activity, a pattern similarily reported in the platypus (Lesku et al. 2011). In another palaeognath bird, "the elegant crested tinamou" (Fig. 3.2), REM sleep and its associated components occurred along with forebrain activation resembling with any other neognath birds so far studied (Tisdale et al. 2017). Nevertheless, the mixed REM sleep state was not found in the tinamou (Tisdale et al. 2017). Furthermore, partial homologies in sleep states of the bearded dragon lizard with the mammals and birds have been reported (Libourel et al. 2018). These studies are able to link to some extent the sequential steps toward the evolution of sleep. It appears that NREM sleep and REM sleep arose from a heterogeneous state having mixed components of slow- and fast-wave activities of high-amplitude waves that temporally segregated into two distinct states.

3.2.2 Melanism, Sleep–Wakefulness, and Cognition in Birds

Melanocytes are pigment-producing cells primarily located in the epidermis, hair, and eyes. Besides these, melanocytes are found in the brain and possibly perform several neuroendocrine functions. In the human brain, a pigment in the brain is called neuromelanin, which has been found primarily in dopaminergic and aminergic groups of neurons in the substantia nigra and locus coeruleus (Bush et al. 2006; Zecca et al. 2002). In the human brain, melanocytes are involved in the release of "prostaglandin D2 (PGD2)" and an endogenous opioid "β-endorphin" (Takeda et al. 2006). The receptors of both PGD2 and opioids are involved in the regulation of sleep–wakefulness (Takeda et al. 2007; Urade and Hayaishi 2000). Does it mean that melanocytes or melanocyte-derived factors would be involved in the regulation of sleep–wakefulness or its rhythm? It is, however, not known clearly, but in one such study on barn owls (*Tyto alba*) (Fig. 3.3), it has been reported that sleep architecture is different in owlets having more dark melanic spots in their feathers compared to less or no melanic spots (Scriba et al. 2014). It has been reported that the ultradian rhythm of sleep–wakefulness was also associated with the melanization in owlets (Scriba et al. 2017). The offspring of the mothers having more dark melanic spots exhibited shorter NREM sleep compared to babies born from the mothers having less dark melanic spots. Also, the heavily spotted male nestlings and the offspring of heavily spotted mothers frequently changed the vigilant states (Scriba et al. 2014). Interestingly, it has also been found that the individuals born from heavily spotted

Fig. 3.2 Elegant crested tinamou (*Eudromia elegans*), one of the ancient birds, does not have the mixed REM sleep state as has been reported in Ostrich. Attribution: Photo by Dominic Sherony / CC BY-SA (https://creativecommons.org/licenses/by-sa/2.0)

mothers exhibit weak strength of behavioral/brain lateralization (Gaillard et al. 2017). It is believed that strongly lateralized individuals are cognitively more successful in performing tasks compared to nonlateralized conspecifics (Plonka et al. 2009). Therefore, it is likely that the birds having different levels of melanin may exhibit different sleep–wake architecture and cognitive ability.

3.3 Sleep in Mammals

Sleep–wakefulness has been characterized in several aquatic and terrestrial mammals. In standard practice, for polysomnographic characterization of sleep state into NREM and REM sleep in mammals, the low-voltage and high-frequency EEG waves associated with the increased motor activity are identified as wakefulness. Epochs with high voltage and low-frequency EEG waves (0.5–4 Hz) and decreased motor activity are characterized as NREM sleep. Epochs with low-voltage and high-frequency EEG waves (4–9 Hz) with a prominent theta peak

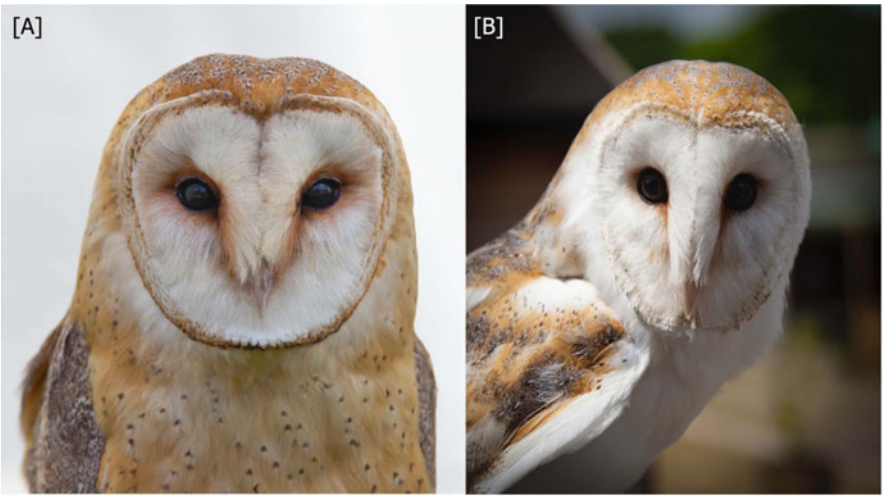

Fig. 3.3 The barn owl (*Tyto alba*) showing two different types of melanic spots. (**a**) The owl has dark melanic spots in their golden breast feathers, while (**b**) the other owl exhibits now dark spots and white breast feathers. The owls with darker melanic spots exhibited shorter NREM sleep compared to owls having less dark or no melanic spots. Attribution: Photo by Mark Broadhurst from Pexels

and nuchal muscle atonia are identified as REM sleep (Jha et al. 2006; Zepelin et al. 2005).

Several factors, including feeding behavior, influence sleep–wake architecture (Gonfalone and Jha 2015; Jha and Mallick 2009, 2011). For example, carnivores, such as the bat and opossum, sleep for 18–20 h a day while the big herbivores, such as the elephant and giraffe, sleep for as little as 3–4 h a day (Jha et al. 2006; van Twyver and Allison 1970; Zepelin et al. 2005). It has been suggested that food habit in mammals correlates significantly with their sleep time (Siegel 2005). Surprisingly, the daily sleep time is highest in carnivores, lower in omnivores, and lowest in herbivores. Although sleep in the herbivores is less, the total sleep time correlates inversely with their body mass; however, similar correlation does not exist in carnivores or omnivores (Siegel 2005). It is not clear why the total sleep is correlated significantly with the body mass of herbivores only. As has been suggested that herbivores face consistent threats from carnivores, therefore, the lower daily sleep amount could be viewed in light of them being in a safe and/or an unsafe environment (Siegel 2005). Interestingly, irrespective of the food habit of animals, the daily sleep amount is highest among the primitive mammals, such as the platypus and ferret, and lowest among the modern mammals, such as the monkey and human (Fig. 3.4) (Jha et al. 2006).

Birds and terrestrial mammals exhibit two distinct sleep states, that is, NREM sleep and REM sleep (Amlaner 1994; Zepelin et al. 2005), whereas mammals that have eventually adapted to an aquatic environment show either little or no sign of

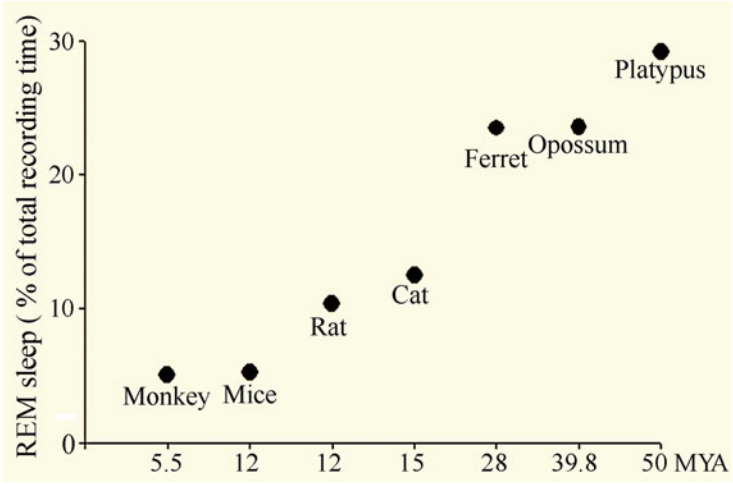

Fig. 3.4 REM sleep amount (percentage of total recording time) in ancient and modern mammals. Please note that the three ancient mammals the "platypus, opossum, and ferret" have the highest amount of REM sleep among the modern mammals. (Taken and modified from Jha et al., Behavioural Brain Research, 2006. Permission obtained from Copyright Clearance Center of BBR for reproduction of the Fig under license # 4835301248808)

REM sleep (Siegel 2005), thus exhibiting almost a unitary nature of sleep. Furthermore, the REM sleep percentage amount in old primitive terrestrial mammals, for example, the platypus (Siegel et al. 1999) and the ferret (Jha et al. 2006), is quite high as compared to the modern mammals (Fig. 3.4). In addition, these two animals exhibit possibly a phenotype of a primitive REM sleep that has been characterized as REM-2 (Fig. 3.5). Interestingly, sleep in fur seals, when they sleep on land, resembles that in the terrestrial mammals; that is, the bilateral EEG exhibits synchronization during NREM sleep and desynchronization during REM sleep and sleep cycle alternates between NREM and REM sleep. However, when fur seals sleep in water, the occurrence of REM sleep reduces exceptionally to the extent that there may not be even a single episode of REM sleep (Lyamin et al. 2002). In fact, it also defies the principle of homeostatic regulation of sleep since no rebound of lost REM sleep is seen when fur seals return to land after staying several weeks in water (Siegel 2005).

Adaptation to the ecological niche may beget changes in the appearance of REM sleep in animals. Although both NREM sleep and REM sleep have been reported in birds, REM sleep episodes in them seem to be shorter in duration than that in mammals (Amlaner 1994; Zepelin et al. 2005), possibly a result of arboreal adaptation. Fishes, amphibians, and reptiles share the physiological correlates of brain waves during the sleep/rest phase, but similar to the aquatic mammals, they do not show any signs of REM sleep (Flanigan 1973; Hartse 1989). Similarly, the echidna (the monotremes), a representative of the earliest branch of mammalian evolution,

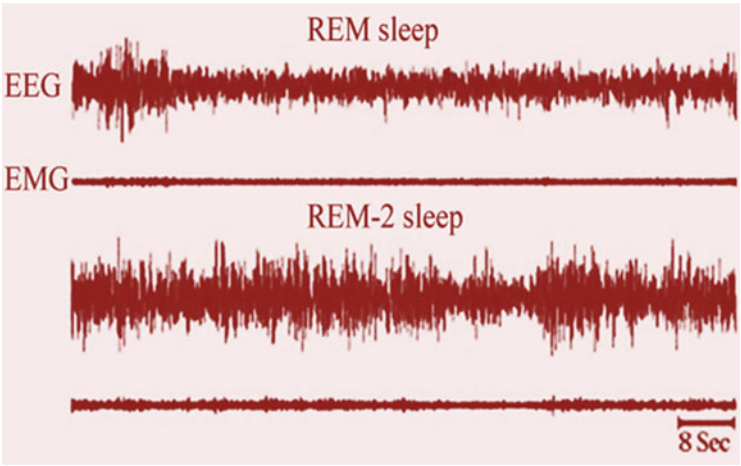

Fig. 3.5 Polygraphic traces during classical REM sleep and high-amplitude and high-frequency REM-2 sleep states in the ferret. Please note that the high-amplitude and high-frequency REM sleep (REM-2) is present in the phylogentically older mammals such as the ferret and platypus. (Taken from Jha et al., Behavioural Brain Research, 2006. Permission obtained from Copyright Clearance Center of BBR for reproduction of the Fig under license # 4835301248808)

neither exhibits REM sleep (Allison et al. 1972) nor has brainstem neuronal activity associated with REM sleep generation (Siegel et al. 1996). Rather, its sleep has features of both NREM and REM sleep states (Siegel et al. 1996). It is likely that some necessary adaptation may not have favored REM sleep in echidna, and it was hence eliminated. Interestingly, in other primitive mammals, for example, the platypus (monotremes) (Siegel et al. 1999) and the ferret (mustelids) (Hsu et al. 2009; Jha et al. 2006; Thurber et al. 2008), a high proportion of REM sleep amount has been recorded. The low amount of REM sleep in modern mammals compared to primitive mammals (Jha et al. 2006) and almost nil or very less amount of REM sleep in mammals such as echidna and aquatic mammals advocate the influence of adaptive forces on REM sleep genesis.

The sleep–wake pattern in aquatic animals such as fishes and amphibians, or mammals such as cetaceans, shows a marked absence of REM sleep. It is known that fishes and amphibians lead an aquatic life, while the limited studies about the sleep pattern in reptiles show that these animals have either adapted to aquatic life (such as the turtle) or live near to the water body (such as black and green iguana lizards). It is likely that the unitary nature of sleep will be observed in animals staying close to or completely adapted to aquatic life. Sleep–wakefulness needs to be examined in depth in reptiles, which absolutely stay away from the water mass. This might give us some clues regarding the evolution of the dual nature of sleep. Furthermore, the cetaceans, which are aquatic mammals, have no REM sleep, and fur seals, which adapt to both terrestrial and aquatic life, exhibit a negligible amount of REM sleep in water. Interestingly, REM sleep can also be artificially abolished in experimental animals (Newman et al. 2008; Rechtschaffen and Bergmann 2002) by using specific

deprivation methods such as disk-over-water and flower-pot methods, in which water is used in the surrounding medium. It raises the following questions: "Is the evolution of REM sleep in vertebrates confined to life on land only and is it that the adaptive force for life in an aquatic environment inhibits the occurrence of REM sleep?" It is possible that REM sleep serves some meaningful purpose only in terrestrial mammals and birds, and hence its evolution is confined to these land species only (Madan and Jha 2012b).

3.4 Unihemispheric/Asymmetrical Sleep

The polysomnographic correlates during wakefulness, NREM sleep, and REM sleep in terrestrial mammals and birds are recorded from both the hemispheres showing bilateral symmetry. However, aquatic mammals, and some birds, show a different sleep behavior. Their one half of the hemisphere sleeps while the other half remains awake. In aquatic mammals such as the dolphin, whale, and manatee, the sleep–wake cycle alternates periodically between the hemispheres. On the other hand, in birds and semiaquatic animals, unihemispheric sleep appears intermittently between bihemispheric sleep. Polysomnographic recordings have shown the appearance of high-amplitude slow-wave activity in one hemisphere conclusively, while at the same time low-voltage, high-frequency EEG waves in another hemisphere. In addition, one eye contralateral to the sleeping brain remains closed, and the eye ipsilateral to the sleeping brain remains opened. Similarly, the flippers of dolphin and whale exhibit the same pattern. The presence of this unique unihemispheric sleep phenomenon clearly suggests that evolutionary forces have greatly modified the sleep pattern depending on the necessity in the species.

3.4.1 Unihemispheric Sleep in Birds

The characteristics of sleep in birds may also depend on the lateralization of brain functions. In domestic chicks, the left hemisphere is possibly involved in the selection of cues allowing stimuli to be classified into categories, while the right hemisphere could be involved in spatial analysis and responses to novelty (Mascetti et al. 2007). Such lateralization could also be associated with the phenomenon of unihemispheric sleep induction (Mascetti et al. 2007). During sleep, birds usually exhibit brief and transient periods in which one eye is open while the other remains shut. Electrophysiological recordings have shown that the hemisphere contralateral to the open eye reveals an EEG with fast waves typical of wakefulness, while the hemisphere contralateral to the closed eye shows an EEG typical of slow-wave sleep. Moreover, bilateral eye closure is associated with bihemispheric slow-wave sleep and REM sleep (Mascetti et al. 2007). Unilateral sleep with unilateral eye closure has been reported in Cape white-eye passerine birds, gulls, European blackbirds, pigeons, domestic chicks, mallard ducks, and several other birds; however, in some birds, it remains undetected [for review, see Mascetti 2016].

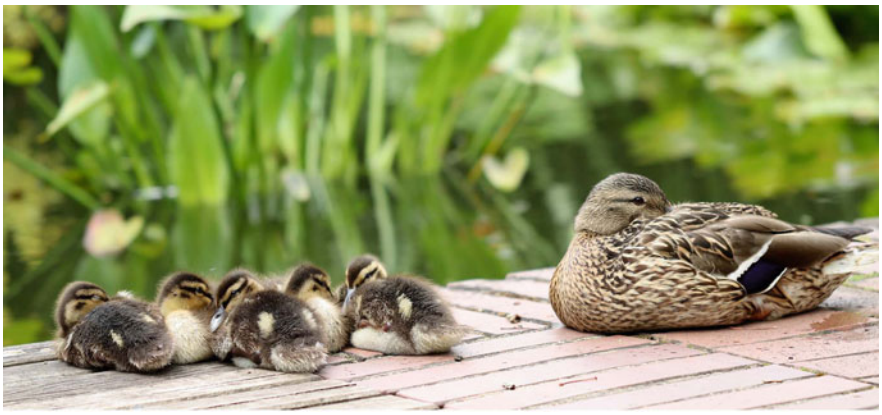

Fig. 3.6 A female mallard duck with her ducklings. Please note that the mother duck is sleeping with one eye open, and at the same time watching her ducklings. Attribution: Image by Annette Meyer from Pixabay

The unihemispheric sleep in birds helps them in long hour flight such as during migration. It has been found that during long hours of migratory flight, the frigate birds slept while flying primarily through unihemispheric sleep (Rattenborg et al. 2016). More episodes of unihemispheric sleep have been found in European blackbirds and domestic chicks, when they sleep with their bill forward position; this means that they are visually observing the surrounding (Mascetti 2016). Similarly, unilateral eye-opening during daytime sleep in Swainson's thrush has been found to be associated with predator detection (Fuchs et al. 2006, 2009). Rattenborg et al. (1999) have reported that a group of mallard ducks sleep in a row, and the ducks sleeping at both the ends of the row exhibited maximum episodes of unihemispheric sleep and unilateral eye-opening, which was directed towards the environment (Fig. 3.6) (Rattenborg et al. 1999). It suggests that unihemispheric sleep in the mallard ducks could be associated with preparedness for the eventualities (Rattenborg et al. 1999). The reports also suggest that unihemispheric sleep plays an important role in hemispheric dominance and also for the dominance in the control of learning behavior (Mascetti et al. 1999).

3.4.2 Unihemispheric Sleep in Mammals

Adaptive forces also influence sleep properties in mammals. Just as arboreal adaptation has greatly influenced avian sleep, aquatic adaptation has altered sleep in the cetaceans (Amlaner 1994; Lyamin et al. 2002). Similar to the unihemispheric sleep of domestic chicks, the cetaceans (aquatic mammals) also exhibit lateralized sleep behavior (Lyamin et al. 2005). Lateralized sleep has been recorded from aquatic and semiaquatic mammals such as bottlenose dolphins, Amazonian dolphins, pilot

whales, beluga whales, eared seals, true seals, and manatees [for review, see Mascetti (2016)]. An asymmetrical EEG with high-amplitude and slow-frequency waves were recorded in one hemisphere (as is found during sleep) and, at the same time, low-amplitude and high-frequency waves in the other hemisphere (as is found during wakefulness) (Mascetti 2016; Mukhametov 1987; Mukhametov et al. 1977; Ridgway 2002). In dolphins, it was observed that they spent almost 75% time in wakefulness during a day in which the recorded EEGs were desynchronized in both the hemispheres. However, during the remaining 25% time, alternating unilateral synchronized EEGs, an accurate sign of sleep, were recorded. The unilateral slow-wave sleep periodically alternated between the hemispheres in a session-wise manner (one hemisphere dominated in one session, and the other dominated in another session), and thus both the hemispheres were engaged in the generation of slow-wave sleep (Mascetti 2016; Mukhametov 1987; Mukhametov et al. 1977; Ridgway 2002).

Absolute aquatic mammals such as dolphins and whales have only unihemispheric sleep, and they do not show bilateral slow-wave high-amplitude EEG. On the other hand, fur seals display two different sleep patterns: bilaterally symmetrical slow-wave sleep when they sleep on land and asymmetrical slow-wave sleep with a striking interhemispheric EEG asymmetry when they are in water (Lyamin et al. 2002). Lyamin et al. have reported that the fur seal exhibited more unilateral slow-wave sleep in water compared to land (Lyamin et al. 2018). They have also observed a unique sleeping posture of the fur seal in water. They have reported that the fur seal keeps its nostrils and three flippers out of the water while paddling with only one flipper to keep the body afloat. An additional interesting observation was that the EEG was desynchronized in the hemisphere contralateral to the paddling flipper (Ungurean and Rattenborg 2018).

In aquatic and semiaquatic mammals, unihemispheric sleep could be a kind of skill developed to survive in an aquatic environment. It might be providing them equal opportunity to breathe and stay vigilant and, at the same time, fulfill their sleep demands, thus benefiting them. The open eye must be allowing them to scan the environment for any possible threat. The existence of such a specific nature of lateralized sleep in aquatic mammals suggests the role of evolutionary adaptive forces in the development and modification of mammalian sleep. It also provides us an insight into "how to develop a skill to sleep under a changing and challenging environment".

3.5 Sleep During Migratory Flights

Several animals, including birds and mammals, migrate, which is often characterized as a regular return movement between breeding and wintering areas. In animals, the migration could be obligate in nature, which means it is "hard-wired or pre-programmed" as the animals leave and return to the breeding area at a specific time of the year, whereas facultative migration is considered optional, occurring in response to prevailing conditions of food or weather (Berthold 2001). Although

several animals migrate, sleep recording during migration has only been studied in birds.

The migratory birds fly continuously for several days. For example, bar-tailed godwit birds migrate from Alaska to New Zealand more than 10,000 km in 9 days. They fly nonstop across the central Pacific Ocean, during which the metabolic rate remains 8–10 times more than the basal metabolic rate (Gill et al. 2009). Similarly, the great frigate birds (Fig. 3.7) fly for months and travel huge distances uninterruptedly (approx. 20,000 km or more) around the Indian Ocean (Bäckman et al. 2017). If the migratory birds remain in flight for days and months, it raises a question about how these birds, over so many days in flight, manage to deal with potential dehydration and sleep deprivation. Do birds eat or sleep during their migratory tour? To satisfy their energy needs, the migratory birds utilize their reserve food during the nonstop flight. But, what about sleep requirements? It has been speculated for a long time that birds may be able to sleep while they are on their wings (Rattenborg 2006a). One of the reports suggests that the frigate birds (Fig. 3.7) sleep during its nonstop flights for approximately 6 days over the Pacific Ocean (Rattenborg et al. 2016). Rattenborg et al. have observed in this study that frigate birds slept for only 2.89% in flight but 53.28% on land. Furthermore, they found that

Fig. 3.7 The great frigate bird flies for days uninterruptedly during migration. Image by Jon Finlay on Unsplash

birds slept more during the night compared to the flight during the daytime (nighttime flight: 5.44% while daytime flight: 0.36%), whereas, on land, the birds exhibited comparable sleep time during day and night (night: 53.76% and day: 47.90%). These data suggest that although birds sleep during the migratory nonstop flight, sleep is drastically reduced. Even the power of the slow-wave activity has also been found to be reduced during the flight. Such a small amount of sleep in migratory birds during the nonstop flights may be comparable with a power nap in humans. As it has been observed in humans that a 30-min nap during the day has refreshing values as it promotes wakefulness as well as performance (Dhand and Sohal 2006). On the other hand, a nighttime nap (120-min nap) increases sleepiness and fatigue, and it reduces performance (Oriyama et al. 2019). Normally, human subjects sleep during the night and remain awake during the day, so only a daytime power nap has a refreshing value. The frigate birds, however, show a comparable amount of sleep during day and night, and therefore, the short nap during the nighttime migratory flight may have beneficial and refreshing effects on birds.

In another study, sleep was recorded in white-crowned sparrows during their migratory and nonmigratory seasons. The birds exhibited approximately two-thirds less time in sleep during the migratory seasons compared to the nonmigrating seasons (Rattenborg et al. 2004). Interestingly, the loss of sleep during the migratory period had no deficit in the performance of the repeated-acquisition task during the migratory season. Nevertheless, one-night sleep-restriction in the same birds during their nonmigratory season caused a significant deficit in their performance in repeated-acquisition tasks. This study clearly demonstrates that sleep loss during the nonmigratory season adversely affects learning and memory, but reduced sleep during the migratory season does not have similar detrimental effects on learning and memory (Rattenborg et al. 2004). Therefore, it appears that sleep loss during migratory and nonmigratory periods has different effects on performance in the migratory birds.

Increased neurogenesis in the hippocampus is one of the underlying mechanisms of enhanced learning and memory (Tripathi et al. 2020). Several reports suggest that the number of hippocampal neurons in the nonmigratory birds is significantly less than the migratory birds (de Morais Magalhaes et al. 2017; LaDage et al. 2011; Pravosudov et al. 2006). In addition, the adult nonmigratory birds exhibit a low density of new hippocampal neurons compared to the migratory birds. Interestingly, the rate of neurogenesis in the adult migratory birds increases during the migratory season (LaDage et al. 2011). Increased neurogenesis during the migratory season possibly maintains high cognitive levels in migratory birds even though they remain sleep deprived (one of the factors that cause memory deficit) during their journey.

3.6 Sleep During Pregnancy and Postpartum

Several studies have reported that sleep quality significantly alters during and after pregnancy. Many physiological, societal, and psychological changes occur during the perinatal and the postpartum periods, which can potentially alter sleep. Among

many, the postpartum childcare responsibility and postpartum depression could be one of the factors that possibly give the mother sleepless time for days. In animals, such as whales and dolphins, mother, as well as calf, both remained active and mobile the whole day during the first postpartum month and did not show sleeping behavior at all, primarily because of an external threat (Lyamin et al. 2005, 2007; Sekiguchi et al. 2006). Similar to avian sleep, cetaceans also exhibit unihemispheric sleep, and it was presumed that whales and dolphins may be active during the postpartum period but must be having a unihemispheric sleep. The unihemispheric sleep has always been found to be associated with the closure of the contralateral eye in the birds and cetaceans. However, surprisingly, the mothers did not show either uni- or bilateral eye closure during the initial 2 months of the postpartum period. The calf, however, showed a significant amount of unilateral eye closure 1 month after birth (Lyamin et al. 2007). It appears that the mother and calf were both almost sleepless for a month. However, it is not clear yet if it would be a kind of evolutionary adaptation to an aquatic environment or just a general event occurring across all higher animals.

Although the cetacean mother and calf were sleepless, in the laboratory rat, mothers were not found to be sleepless during postpartum. In the laboratory, when sleep is recorded in female Wistar rats during pregnancy and postpartum, it is observed that although the animals showed frequent intermittent arousal from sleep, NREM sleep and delta power during NREM sleep, significantly increased, particularly during the circadian timing of sleep (Sivadas et al. 2017). The mother rats clearly showed an increased level of anxiety during the third trimester of pregnancy, which gradually improved after parturition (Sivadas et al. 2017). In addition, it has been observed that the mother rats attempted to synchronize sleep–wake timing along with maternal care. The mothers were sleeping mostly in NREM sleep when nursing the pups. Sleep was highly fragmented during nursing, but sleep depth was comparable to the nonnursing time periods (Benedetto et al. 2017). These studies suggest that there is an obvious compromise in the sleep–wake cycle, but it is always associated with some compensatory reappropriation.

In humans, sleep deficit is very common among pregnant and postpartum women. Sleep disorders such as frequent arousal and nighttime waking, poor sleep quality, more daytime napping, insomnia, restless leg syndrome, snoring, and sleep apnea are markedly common during pregnancy in women (Facco et al. 2010; Okun and Coussons-Read 2007). The older maternal age has been found to be having a higher prevalence of poor sleep quality compared to the young mother (Yang et al. 2020). The cause of sleep deficit during pregnancy can primarily be attributed to hormonal changes such as estrogen and progesterone during pregnancy (Sowers et al. 2008). In addition, some challenging demands during pregnancy, such as a developing fetus inside the womb, demands space, which causes respiratory and micturition discomfort to mother, and these may affect the overall sleep during pregnancy. Some women develop depression, anxiety, and antepartum suicidal ideation during pregnancy and the postnatal period (Gelaye et al. 2017). Surprisingly, the sleep timing during pregnancy and postpartum periods is highly correlated to the development of postpartum symptoms of mania, depression, and obsessive-compulsive disorder

(Obeysekare et al. 2020). Obeysekare et al. divided the participants into "early and late sleeper" groups (the early group was sleeping before 11:30 PM, and the late group was sleeping after 11:30 PM). They found that the late sleeping women had a higher prevalence of developing symptoms of mania, depression, and obsessive-compulsive disorder in the postpartum period (Obeysekare et al. 2020). Besides these, a strong correlation between mothers' postpartum sleep disturbance with mother–infant interaction has been found. The mothers having poorer sleep continuity had reduced maternal sensitivity and caregiving attitudes toward their infants at their home (King et al. 2020). These studies suggest that sleep disturbances are common during pregnancy and postpartum across all mammalian species. Some may reappropriate the loss through the compensatory mechanism, and some may not. If it is not compensated, the maternal sleep disruptions may have long-lasting consequences on the child's psychological health.

3.7 Normative Aging Associative Sleep Disturbances

Sleep plays an essential role in maintaining our health and cognition (Chowdhury et al. 2011; Kumar and Jha 2017; Madan and Jha 2008, 2012a; Qureshi and Jha 2017; Qureshi et al. 2019; Tripathi and Jha 2016, 2019; Tripathi et al. 2018, 2020). However, altered sleep is a common problem in normative aging subjects. Sleep alteration occurs at both the micro- and the macrolevels in the aged subjects. At the microlevel, the deficits are found in sleep quality and their oscillatory waves, whereas, at macrolevels, sleep is altered at an architectural level such as sleep efficiency, total sleep time, NREM and REM sleep ratio, and episode length of NREM and REM sleep (Lavoie et al. 2018; Mander et al. 2017). Some of the noticeable changes in sleep architecture with advancing age are (1) circadian alteration in sleep timing (early bedtimes and rise times), (2) sleep-onset latency, (3) sleep fragility, (4) reduced NREM sleep amount (more time spent in N1 and N2 sleep stages and less in N3), and (5) reduced NREM–REM sleep cycles (Conte et al. 2014; Ohayon et al. 2004; Redline et al. 2004; Van Cauter et al. 2000). The daytime-nap frequency and sleep urge also increase in older adults, which is surprisingly linked to the presence of comorbid conditions such as depression, pain, and nocturia (Foley et al. 2007; Vitiello 2009).

The elderly subjects also demonstrate altered amplitude of circadian clock for some endogenous rhythm such as body temperature and melatonin rhythms, and it could be one of the factors underlying the age-related sleep disturbances (Dijk and Duffy 1999; Munch et al. 2005). The aged person experiences a weak wake-inducing circadian signal during the evening and increased sleepiness during the wake-hours, especially during the late afternoon (Strogatz et al. 1987). Some of the older adults show a preference for morningness, which could primarily be because of phase advancement of the circadian oscillator (Brown et al. 2011). In addition, a linear reduction in NREM sleep accompanied by a decrease in the amplitude of delta waves and evoked K-complex with increasing age suggests gross architectural

changes in homeostatic and circadian regulatory machinery of sleep–wakefulness with aging (Bliwise 1993; Colrain et al. 2010).

Sleep plays an important role in the modulation of the neuroendocrine system. The growth hormone from the pituitary gland is released during early sleep. An interesting study by Van Cauter et al. in a cohort of 149 subjects found that the sleep amount exponentially decreased from adulthood to midlife (36–50 years) and late-life (71–83 years). Interestingly, the alteration in NREM sleep and sleep fragmentation from early adulthood to midlife to late-life was associated with a parallel decrease in growth hormone secretion, along with an elevation in evening cortisol levels (Van Cauter et al. 2000). They have also found that the elevated evening cortisol level was associated with age-related decline in the REM sleep amount (Van Cauter et al. 2000). Another pituitary hormone, thyroid-stimulating hormone (TSH), exhibits a circadian oscillatory secretary pattern. The level of TSH remains low during the daytime, and increasing trends start during the late afternoon, which peaks at sleep onset. The level of TSH declines gradually in the night and returns to its low level during the day. Although TSH secretion shows the circadian-cyclic pattern, it is also associated with sleep–wakefulness. A few studies have shown that the nocturnal decrease in TSH secretion is associated with sleep, while the daytime increase is associated with wakefulness (Li et al. 2018). Therefore, it is likely that the altered sleep–wake cycle in the elder may influence the level of circulating TSH, which may, in turn, cause "subclinical hypothyroidism" and homeostatic ionic imbalance (Aggarwal and Razvi 2013; Mir et al. 2019). Moreover, several studies have shown that the subclinical hypothyroidism condition adversely affects cardiovascular and cognitive functions and causes depression and disability (Aggarwal and Razvi 2013). Taking all these pieces of evidence together, it is apparent that if not all but some aging-associated decrease in health and cognition could be attributed to poorer sleep quality (Aggarwal and Razvi 2013; Gadie et al. 2017). On the other hand, a study, conducted by "Estee Lauder company," has clearly demonstrated that the poor sleeping pattern increases aging, especially skin and poor recovery from the environmental stressors, for example, breakdown of the skin barrier from ultraviolet radiation (Schrom et al. 2019).

It has been demonstrated beyond doubt that disturbed sleep in normative aging compromises health. On the other hand, it is also true that reduced sleep is a normal part of aging. Now it is pertinent to ask whether elderly subjects need more sleep than they are usually able to obtain. Sleep architecture changes as we grow old, but poor sleep, frequent arousal, and waking up tired almost every day are not part of normal aging.

3.8 Conclusion

Several pieces of evidence suggest that sleep exhibits progressive phylogenetic development as well as inter- and intraspecies variations. Phylogenetically, the lower vertebrates such as fishes, amphibians, and reptiles exhibit a simpler form of sleep. On the other hand, birds and mammals show a complex dual nature of sleep

characterized as NREM and REM sleep. Interestingly, the aquatic animals, which have gone back from land to water for their survival, have eliminated REM sleep (Madan and Jha 2012b). We still do not know why REM sleep evolved in birds and mammals and why it was eliminated in the aquatic mammals. Furthermore, birds and aquatic mammals have evolved a unique "single-hemispheric sleep" during which one hemisphere sleeps while the other remains awake. Such evolutionary adaptation in sleep is best suited for their survival as they can perform a difficult task (of long-distance nonstop migration/an air-breather living in water) while asleep. Sleep can be compromised drastically but temporarily during pregnancy and postpartum, or chronically reduced with aging, but nature always reappropriates the sleep loss in some manner. These studies, nevertheless, provide us an insight into "how to develop a skill to sleep in a changing and challenging environment". We sustain our life in the current challenging world, where we experience insufficient sleep, poor sleep quality, frequent arousal, and waking up tired almost every day. A sleepless society cannot be healthy and productive. Sleep disruption also costs our reproductive efficiency (Goldstein and Smith 2016) and, ultimately, our survival. Therefore, it is essential to learn from birds and aquatic mammals on how to develop skills and strategies for sleep management.

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Sleep Loss: What Does It Do to Our Brain and Body?

4

Abstract

It is nowadays a common practice to "work without sleep and catch up later." It is not a good idea to keep up with sleep deficit. In recent years, several reports have shown that the consequences of chronic sleep loss are not reversible. It may cause impairment in neuronal functions and neurodegeneration. The energy expenditure, risk of hypertension, cardiovascular disease increases, and the immune system diffuses into a compromised state during sleep deprivation. Sleep deprivation may cause the deposition of toxic metabolites usually produced during long hours of wakefulness. It may impair neurological functions and cause the death of brain cells. Sleep loss is affecting the health of children, adults, and elderly people. The brain shrinks, and the body becomes vulnerable to diseases. It affects the brain and neural development in children too. It is an irony that though its implications are gradually becoming clear, still it is turning out to be an epidemic in our modern society. Sleep loss can become a liability for the people having unusual lifestyles, working for long hours, in the night shift, and the subjects suffering from chronic sleep disorders. Here, we review some evidence to appraise the understanding of the known changes in our brain and body after prolonged sleep deprivation.

Keywords

Brain maturation · Cardiovascular disease · Immunity · Metabolic disorders · Obesity · Sleep deprivation

4.1 Introduction

Sleep deprivation constitutes a direct experimental approach to understand the different aspects of sleep physiology. Total sleep loss is known to influence several behavioral correlates, such as irritability, anxiety, inability to concentrate, and

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learning and memory. Furthermore, sleep-deprived animals show symptoms of fatigue, skin lesions in paws, ulceration in gastrointestinal tracts, and so on. Despite a considerable increase in food intake and metabolic rate, body temperature and body weight decrease in sleep-deprived animals (Rechtschaffen et al. 1989). Although the deprivation-induced effects in the brain and body accumulate in proportion to the extent of deprivation, the effects subside when the animal is allowed to sleep again. Chronic sleep disturbances have also been linked to the progression of a number of disorders, including narcolepsy, Alzheimer's disease, Parkinson's disease, and depression.

Initial experiments to investigate the effects of sleep deprivation were performed on animals in 1894 by Marie De Manacéine (Bentivoglio and Grassi-Zucconi 1997). She found that puppies died after 4–6 days of sleep deprivation. At the end of the study, there was marked hypothermia, capillary hemorrhages, and the red blood cell count decreased from 5 to two million. However, the red blood cell count subsequently increased. In another study, three adult dogs were kept awake by making them walk when necessary, and the dogs died after 9, 13, and 17 days (Tarozzi 1899). In yet another study, several dogs were deprived of sleep for periods varying from 30 to 505 h, but not beyond the point where they showed extreme sleepiness (Legendre and Pieron 1913). In this study, the dogs did not die, possibly because they were not deprived beyond a limit that they could not recover. In both of the latter studies, histological preparation of the brain showed diffuse chromatolysis and vacuolization in the neurons. The investigators also observed differences in the viscosity and density of the blood before and after sleep deprivation. All these studies suggest that sleep is indispensable, and its chronic disturbances increase the risk of morbidity.

There are several reasons to believe that chronic sleep deficit is detrimental to the central and peripheral systems. Reports suggest that the brain and bodily systems are very susceptible to the effects of insufficient sleep. Secondly, chronic sleep loss is closely linked to all major neurological and psychiatric conditions such as schizophrenia, Alzheimer's disease, anxiety disorders, and addiction disorders. Our knowledge about the ill effects of sleep disturbances has substantially increased in the past few years, but yet chronic sleep disturbance is an epidemic in our modern society. Here, we have discussed a few but essential facets of the consequences of chronic sleep loss.

4.2 The Effects of Sleep Loss on the Brain

How does chronic sleep loss affect our brain remains an intriguing question. Reports suggest that chronic sleep deprivation affects several systems in the brain, such as the oculomotor system, brain development, and brain circuitries. It is very important to understand (a) the changes that occur at the brain level after chronic sleep deprivation and (b) how chronic sleep deprivation is linked with the onset of neurological disorders. Here, we have attempted to gather some evidence, which can update our understanding of the long-term consequences of chronic sleep disruption.

4.2.1 Chronic Sleep Loss Affects Brain Maturation

The brain sensory neuronal circuitries remain in naïve form at the time of birth, and postnatal maturation of sensory pathways is dependent on stimulus-driven neuronal activity (Hubel and Wiesel 1970) and sleep (Madan and Jha 2008). Altered visual experience during the critical period after birth in kitten permanently impaired the physiologic responses of the brain to visual stimulation. During the time of development, synaptic connectivity in the cortex exhibits a high level of plasticity as synapses are formed and retracted, a process strongly driven by sensory activity (Hubel and Wiesel 1970). We have reported that sleep potentiates the processes for the formation of new connections as well as the retraction from the altered pathways in the visual circuitry (Aton et al. 2009; Jha et al. 2005). As little as 6 h of sleep is sufficient enough to enhance the circuit re-modulation induced by monocular deprivation in the visual cortex, and this process is blocked when animals are prevented from sleeping (Frank et al. 2001) or when postsynaptic activity in the visual cortex is reversibly silenced during sleep (Jha et al. 2005). We further demonstrated that sleep potentiates the synaptic strengthening through the activation of the glutamatergic NMDAR receptor and protein-kinase activity, the key components of sleep-dependent remodeling of synaptic connections (Aton et al. 2009). These studies suggest that sleep is one of the functional entrants that helps matured naïve circuitries to an adult form. Since mammalian sleep in not a homogeneous state, it may be asked if other states have similar functional properties. We have observed that both NREM and REM sleep states play a similar role for synaptic remodeling in the visual circuitry (Aton et al. 2009); however, REM sleep alone can play some differential roles in brain maturation.

Consistent evidence about the role of REM sleep in brain maturation has been obtained from REM sleep deprivation studies (Marks et al. 1995). It has been found that in kittens born with normal vision, if the vision in the one eye is blocked for 2 weeks and they are simultaneously devoid of REM sleep during this period, such conditions induced anatomically and functionally deleterious effects on the lateral geniculate nucleus (LGN) in the thalamus (Marks et al. 1995). The effect of REM sleep deprivation in un-occluded kittens resulted in a higher magnitude impact than the one induced by occluding vision in one eye, suggesting that REM sleep deprivation during neuronal circuit development impairs the process of circuit maturation (Marks et al. 1995). Furthermore, it has also been demonstrated that the elimination of ponto-geniculo-occipital waves, a phasic activity during REM sleep, induced similar results in the LGN (Shaffery et al. 1999). REM sleep deprivation delayed the development of synaptic plasticity in the LGN (Hogan et al. 2001) and retarded the maturational reduction of long-term potentiation (LTP) in the visual cortex of immature rats (Shaffery et al. 2002). These results show that REM sleep is also an important part of the development of brain circuitries after birth. The formed circuitries once get matured stay for a lifetime. Therefore, sleep during the initial period seems to be acting like a reinforcer for circuit formation and brain maturation. Not only does sleep help strengthen circuitry during early life, but it also helps

potentiate synapses during the rest of life to maintain the ultimate functionality of the neurons (Madan and Jha 2008).

4.2.2 Chronic Sleep Loss Alters Brain Mass

A lack of sleep may cause brain atrophy. Studies suggest that poor sleep quality is associated with widespread atrophy in the frontal, temporal, and parietal cortices (Sexton et al. 2014; Spira et al. 2016). Surprisingly, the frontotemporal gray matter atrophy has also been noticed in the older normal subjects with excessive sleepiness (>7 h) (Spira et al. 2016). Also, the concentration of gray matter in the brain of obstructive sleep apnea (OSA) patients (having excessive sleep disturbances) significantly reduces (Joo et al. 2010). In these patients, the severely affected brain areas are superior frontal gyrus, caudate nucleus, thalamus, amygdalo-hippocampal areas, and inferior temporal gyrus, where the concentration of gray matter significantly decreased (Joo et al. 2010). These brain areas are essentially associated with the memory function, mood, cardiovascular, and autonomic regulation. The sleep-deprived subjects suffer from memory deficit, cardiovascular dysfunction, mood disorder, and so on, and the underlying cause of these deficits could be attributed to these morphological abnormalities.

Sleep also plays an essential role in neuroprotection. The aggregation of β-amyloid (Aβ) and tau proteins in the brain causes neurodegeneration. It has been observed that sleep is involved in the regulation of β-amyloid (Aβ) levels in the brain (Holth et al. 2019; Shokri-Kojori et al. 2018). The chronic sleep deprivation increases the incidences of Aβ plaque formation (Holth et al. 2019; Shokri-Kojori et al. 2018). In addition, sleep influences the level of tau protein in interstitial and cerebrospinal fluids (Holth et al. 2019). During waking, the tau level increased by 90% in interstitial fluids compared to the sleep state in mice. Moreover, this increase was 100% during sleep deprivation in mice and 50% in humans (Holth et al. 2019). Therefore, it appears that the levels of Aβ and tau proteins significantly increase if the subjects experience excessive chronic sleep disturbances. The deposits of Aβ plaques and tau protein neurofibrillary tangles are associated with neurodegeneration. The Aβ plaque deposits influence the formation of tau protein tangles in the brain, and the tau tangles then initiate the neurodegeneration process, which ultimately leads to Alzheimer's and Parkinson's diseases. In Parkinson's patients, the loss of gray matter begins first in frontal lobes, which further extends to the temporal, occipital, and subcortical areas (Burton et al. 2004). It is not known if sleep deficit contributes to the progression of brain atrophy in Alzheimer's and Parkinson's patients. However, chronic sleep deprivation causes the formation of Aβ plaques and tau protein tangles, which ultimately leads to neurodegeneration.

The prolonged sleep restriction activates microglia and their phagocytic activity, which can lead to brain damage (Bellesi et al. 2017, 2015). Some of the glial phagocytosis-associated genes are upregulated after sleep deprivation (Bellesi et al. 2015). Astrocytes start approaching close to the synaptic cleft during sleep deprivation or extended wakefulness (Bellesi et al. 2015). In the larger synapses, the

astrocytic phagocytosis increases after chronic sleep loss (Bellesi et al. 2017). The signs of enhanced microglial activation and phagocytosis of synaptic elements were found in the chronic sleep-restricted group, while the activity was absent in the acute sleep-deprived group (Bellesi et al. 2017).

Sleep loss also alters the cerebral blood flow and may damage the brain. A significant alteration in resting cerebral blood flow has been recorded in some of the brain areas in the sleep-restricted subjects. The cerebral blood flow significantly reduced in some of the brain areas such as the basal forebrain, right frontoparietal, and cingulate cortices in the drowsy individuals (Poudel et al. 2012). The changes in the cerebral blood flow did not change in nondrowsy subjects. These studies demonstrate that chronic sleep loss may cause brain damage by activating microglia and altering cerebral blood flow.

4.3 The Effects of Sleep Loss on Body System Dysregulation

Insufficient sleep or sleep deprivation may have extreme consequences on metabolic and physiological functions of the body. The chronic sleep deprivation is intricately related to metabolic dysregulation mainly by altering the immune system, sympathetic regulation, neuroendocrine and hormonal coordination, and so on. Consequences of altered sleep on physiological and behavioral states are being recognized reasonably, but still, a lot more understanding is required. Therefore, it is imperative to discern how chronic sleep loss may cause immune and metabolic dysfunctions.

4.3.1 Prolonged Sleep Loss Transiently Suppresses the Immune System

Chronic sleep loss may cause medical conditions, sickness, and weak immunity. In one of the early studies in the 1960s, a 27-year-old young radio jockey in the USA wanted to break the previous "wakeathon" record of 212 h. He volunteered to be a part of the sleep research group in Detroit, USA. At the end of his 220 h of wakeathon, the subject was overly irritated and demonstrated episodic rage, visual hallucinations, and paranoid thinking. The body's emergency energy mobilization failed, and radioactive phosphorus was observed in his blood. His hypothalamic-pituitary-adrenal axis (HPA axis) exhibited an alarming signal of resistance and exhaustion (Luby et al. 1960). Later on, almost similar incidences were observed in animal studies as well. The prolonged sleep deprivation in healthy rats induced hypercatabolic activities, symptoms of secondary malnutrition, and death (Everson 1993). The blood culture examination showed invasion by various lethal opportunistic microbes such as *Pseudomonas*, *Corynebacterium*, *Staphylococcus*, and *Bacillus* strains in the sleep-deprived rats (Everson 1993). It should be noted that under normal conditions, these facultative organisms do not cause primary bacteremia (Relman and Falkow 1995). The life-threatening situations after prolonged

sleep deprivation were attributed to the weakening of the host defense machinery against microorganisms (Everson 1993). Chronic sleep deprivation caused the incursion of pathogenic bacteria during the first few days of sleep deprivation. During the course of sleep deprivation, bacterial overgrowth was observed in the intestine, lymph nodes, and extraintestinal body tissues (Everson and Toth 2000). The chronic sleep deprivation induced internal septic conditions and massive energy imbalance in the body, which may facilitate the invasion of lethal bacteria in the bloodstream (Everson 1995; Everson and Toth 2000; Luby et al. 1960; Shpata et al. 2013). The findings indicated that the processes underlying bacterial disease begin early at the onset of prolonged sleep deprivation, and infection to the normally sterile tissues preceded overt signs of morbidity (Everson and Toth 2000). The precise reason for death after prolonged sleep deprivation is difficult to determine. However, it appears that death may be primarily because of compromised immunity, which facilitates the invasion of opportunistic lethal microbes (Everson 1993). Therefore, it appears that the immune system diffuses into a compromised state after prolonged sleep deprivation and makes the subjects susceptible to infection and sickness.

4.3.2 Prolonged Sleep Loss Alters the Properties of Immune Cells

Sleep deprivation may alter the properties of immune cells in the body. Several studies have demonstrated that prolonged sleep deprivation alters the amount of several immune cells in the body. The numbers of natural killer (NK) cells and other lymphocytes either decreased (Boyum et al. 1996; Dinges et al. 1994; Ozturk et al. 1999; Palmblad et al. 1979) or increased after prolonged sleep deprivation (Born et al. 1997). Whether the number of immune cells will increase or decrease depends on the time span of sleep deprivation. The numbers of T helper (TH) cells and NK cells decreased after 40 h of sleep deprivation, but their numbers increased after 64 h of sleep deprivation (Dinges et al. 1994). Therefore, it is possible that the extent of sleep deprivation may differentially influence the systemic presence of immune cells.

Not only does the prolonged sleep deprivation change the number of immune cells, but it also influences their functional properties. Reports suggest that sleep deprivation also altered the mitogen-induced lymphocyte proliferation (Born et al. 1997; Palmblad et al. 1979). Moreover, the NK-cell lytic activity decreased with short-term sleep deprivation (Irwin et al. 1994, 1996) but increased with prolonged sleep deprivation (Dinges et al. 1994). The phagocytic properties of the immune cells also altered with prolonged sleep alteration (Palmblad et al. 1976). Not only does sleep deprivation alter the proliferation rates of immune cells, but it also alters the tumor growth rate. In one of the interesting studies, Bergmann et al. have found that compared to the control animals, the size of the tumor remained significantly small in the sleep-deprived rats during the initial days of deprivation (Bergmann et al. 1996), but during the later days of deprivation, the size of the tumor grew faster and reached the peak quickly in sleep-deprived rats compared to the control animals

(Bergmann et al. 1996). Therefore, it appears that prolonged sleep deprivation alters the proliferative and phagocytic properties of immune cells.

4.3.3 Prolonged Sleep Loss Alters Immunogenic Responses

Sleep may facilitate the production and redistribution of lymphocytes in the lymph nodes and selectively enhance their immunogenic properties (Besedovsky et al. 2012). The activated lymphocytes (a subset of cells present in the lymph) induce cellular cytotoxicity/immunogenic responses against invading pathogens. The natural killer cells (NK cells are involved in innate immunity) and T cell (cell-mediated response) lymphocytes induce cytotoxicity, whereas B lymphocyte cells are involved in antibody-driven humoral responses. The B cells produce antibodies in response to pathogens, whereas T cells exhibit variable responses. For example, T helper cells produce cytokines and modulate inflammatory responses. The cytotoxic T cells produce toxic granules and induce the death of pathogen-infected cells. Several reports suggest that sleep deprivation may alter the immunogenic responses of various lymphocytes against the pathogen (Besedovsky et al. 2012; Ibarra-Coronado et al. 2015). The 24 h sleep-deprived animals were infected with parasite "*Trichinella spiralis*" larvae. It was found that the mesenteric lymph nodes and spleen exhibited differential effects in sleep-deprived (SD) animals. The number of NK cells and B cells (CD45) increased while the number of cytotoxic T cells decreased in the spleen. At the same time, the numbers of only NK cells increased in the mesenteric lymph nodes in the uninfected SD animals. On the other hand, the cell population in the spleen did not change in the infected non-SD animals, but the number of B cells (CD45) increased in the spleen in the infected SD rats. However, the number of NK cells decreased while the number of T helper (CD4) cells increased in the infected SD animals compared to the infected non-SD animals. These findings clearly suggest that sleep deprivation induces altered immune response against *T. spiralis* infection (Ibarra-Coronado et al. 2015). Boyum et al. have reported that the serum level of immunoglobulins (IgG, IgA, and IgM) significantly decreased in sleep-deprived subjects (Boyum et al. 1996). In normally sleeping subjects, the antibody response against hepatitis-A vaccination was much ameliorated compared to the subjects experiencing disturbed sleep (Lange et al. 2003). These findings suggest that sleep may, directly or indirectly, modulate the immune response against infection/pathogens.

The levels of immune parameters in the body significantly correlate with the timing of sleep–wakefulness (Besedovsky et al. 2012). For example, the levels of proinflammatory cytokines remain high during early nocturnal sleep, but numbers of circulating immune cells and anti-inflammatory cytokines remain high during the awake condition (Besedovsky et al. 2012). The numbers of monocytes, NK cells, and counts of all lymphocyte subsets were significantly low in nocturnally sleeping subjects compared to the subjects who remained awake at night (Born et al. 1997). The count of these cells significantly increased after sleep during the day compared to the nocturnally awake subjects. In addition, sleep plays an essential role in

facilitating the production of "IL-2" anti-inflammatory cytokine. However, it does not influence the production of proinflammatory cytokines such as TNF-alpha and IL-6 (Born et al. 1997). The changes in the concentration of anti-inflammatory cytokines thus seem to be closely linked to the sleep timings.

Cytokines may also, in turn, influence sleep manifestation. For example, micro-injection of IL-1 in the prostaglandin D2-sensitive subarachnoid space in the ventral part of the anterior basal forebrain significantly increased NREM sleep, but REM sleep was decreased (Terao et al. 1998). IL-1-induced NREM sleep was blocked by the cyclooxygenase (COX) inhibitor, suggesting that it may be modulated through COX-2-mediated prostaglandin production in the subarachnoid area (Terao et al. 1998). Microinjection of TNF-alpha in the preoptic area of anterior hypothalamus also significantly increased NREM sleep in rats (Kubota et al. 2002). Furthermore, IL1/TNF microinjections into the locus coeruleus facilitated the expression of NREM sleep (De Sarro et al. 1997). Studies suggest that IL1 may be directly modulating the expression of sleep by altering the sleep-wake-associated neuronal activity (Alam et al. 2004). IL1 enhances the firing rates of NREM-active neurons and inhibits wake-active hypothalamic neurons (Alam et al. 2004). These data suggest that IL1 and TNF modulate sleep by directly acting on sleep circuitries.

On the other hand, sleep deprivation alters the levels of cytokines in the body. Sleep deprivation enhances the production of TNF-alpha and IL-1β and decreases the production of IL-2 after phytohaemagglutinin and bacterial "lipopolysaccharide"-mediated immune response (Uthgenannt et al. 1995). The levels of other cytokines, such as fibroblast growth factor-basic, leukemia inhibitory factor, and interferon-γ-induced monokines, also decreased after 48 h of total sleep deprivation in mice (Yang et al. 2016). Several other cytokines such as macrophage colony-stimulating factor, macrophage inflammatory protein-2, platelet-derived growth factor-bb, and vascular endothelial growth factor did not alter after prolonged sleep deprivation (Yang et al. 2016). In a few studies, the plasma cytokine levels have directly been measured after sleep deprivation. It was found that the normal rising pattern of IL-6 levels at sleep onset was delayed by sleep deprivation (Redwine et al. 2000). Interestingly, an IL-6 level increased after prolonged sleep deprivation (5 days), but the level was overturned with a daily 2-h nap (Shearer et al. 2001). Collectively, all these data clearly demonstrate that the immune system and sleep machinery are strongly interconnected.

Direct evidence is still lacking to establish if chronic sleep loss could be associated with the etiology of diseases and metabolic disorders. Nevertheless, prolonged sleep deprivation induces cachexia and diffuses the immune system into a compromised state without preexisting sickness. It is possible that either sleep loss may be aggravating the deteriorating health or it may have the same diagnostic symptoms found in diseased conditions. After taking the entire evidence (as mentioned above) into consideration, it is highly likely that the chronically sleep-deprived humans could be the immunocompromised subjects.

4.3.4 Prolonged Sleep Loss and Increased Risk of Obesity and Diabetes

Several epidemiologic studies have demonstrated a close link between chronic sleep loss and changes in basal metabolic rate, which are ultimately involved in inducing obesity and diabetes [for review, see Knutson and Van Cauter 2008]. The energy status in the body is regulated by the hypothalamic neurons through the leptin hormone, which is released from the adipocytes (Ahima et al. 2000). Circulating leptin levels in humans show a rapid decline or increase in response to acute caloric shortage or surplus, respectively (Ahima et al. 2000). The total sleep deprivation induces the changes in circulating leptin level (Morselli et al. 2010). Leptin acts as a feedback signal from adipose tissue to the hypothalamus for long-term regulation of energy balance; hence, the alteration of its release with sleep loss may affect the body mass significantly (Mullington et al. 2003). Another peptide, ghrelin, produced predominantly by the stomach, is also involved in energy balance regulation. Leptin induces satiety by activating hypothalamic neurons associated with food intake (Morselli et al. 2010), whereas ghrelin stimulates appetite (Havel 2001). The reciprocal interaction between these two hormones thus helps maintain a balance of our meal consumption. The studies suggest that the decrease in the level of leptin or increase in the level of ghrelin causes obesity and also alter glucose tolerance (Morselli et al. 2010). Interestingly, it has been noticed that one-night sleep deprivation induces subjective hunger (Schmid et al. 2007). Thus, it appears that sleep loss may downregulate the satiety hormone "leptin" and upregulate the appetite-stimulating hormone "ghrelin".

Chronic sleep loss can alter cellular biochemical as well as metabolic processes. Kuhn et al., using an oral glucose tolerance test (OGTT), compared glucose tolerance before and after a prolonged period of total sleep deprivation in the same subject. They observed an altered glucose tolerance during sleep-deprived conditions compared to the normal sleeping subjects (Kuhn et al. 1969). In another similar study, it was noticed that the activity of the enzymes associated with energy metabolism, such as glycolysis and Kreb's cycle in the skeletal muscle, decreased after sleep loss, suggesting that sleep loss initiates a prediabetic type of muscle metabolism (Vondra et al. 1981). Interestingly, they have also noticed an increase in fasting blood glucose levels at the end of the sleep deprivation period (Vondra et al. 1981). The fasting insulin level (blood glucose regulating hormone) and the insulin response to OGTT both increased after sleep deprivation, suggesting that sleep deprivation induces insulin resistance (Spiegel et al. 2009; VanHelder et al. 1993). This evidence suggests that prolonged sleep loss may contribute to increasing the risk of obesity and/or diabetes by altering the enzymatic and/or hormonal activity.

4.3.5 Prolonged Sleep Loss and Increased Risk of Hypertension and Cardiovascular Disease (CVD)

Sleep loss may also trigger obesity and/or diabetes, which may further lead to the prevalence of hypertension and/or cardiovascular diseases (CVDs). Several studies have analyzed the longitudinal impact to determine whether or not short sleep duration increased the incidence of hypertension in insomniac subjects (Nagai et al. 2010). It was observed that the subjects having less than 5 h sleep per night manifested increased risk of hypertension in the middle-aged group but not in the old-aged group (Gangwisch et al. 2006). Furthermore, Irwin and Ziegler in 2005 performed sleep deprivation in normal and alcoholic subjects. They observed that heart rate, blood pressure, and sympathetic catecholamine levels were similar in normal and alcoholic subjects (after alcohol abstinence), but partial sleep deprivation during night induced a greater increase in heart rate in alcohol-dependent men compared to the normal subjects (Irwin and Ziegler 2005). On the other hand, the partial late night sleep disruptions in the normal healthy young volunteers significantly increased the nocturnal level of circulating norepinephrine and epinephrine compared to their undisturbed sleep periods (Irwin et al. 1999). These two circulating hormones increased the vasomotor tone of the blood vessels and increased blood pressure. Additionally, these two hormones/neurotransmitters directly increase the heart rate by accelerating the heart pumping mechanism. Hence, it seems that short sleep duration increases the sympathetic nervous system activity that, in turn, increases blood pressure (Nagai et al. 2010). Furthermore, it has been found that the person who works more than 67 h or more has highest prevalence of coronary heart disease and acute myocardial infarction (Buell and Breslow 1960; Netterstrom et al. 1999). These studies clearly suggest that chronic sleep disturbance hyperactivates the sympathetic nervous system and increases the circulating norepinephrine and epinephrine level, which may lead to an increased risk of hypertension and CVDs.

The prevalence of hypertension is greater in patients with a sleep breathing disorder, such as obstructive sleep apnea (OSA) (Wolk et al. 2003). In OSA patients, there is a recurrent episode of cessation of respiratory airflow due to upper airway inspiratory collapse during sleep. This causes intermittent blockage of air passage through the trachea and ultimately decreases the oxygen saturation during sleep. Sleep gets disturbed with the inspiratory blockage, and patients suffering from OSA experienced significantly less sleep. Several cross-sectional and longitudinal studies have observed that OSA patients manifest a greater chance of the occurrence of hypertension [for review, see Wolk et al. 2003]. The association between sleep-disordered breathing and hypertension has been observed in men and women across all ages (older and younger subjects) and ethnic groups (in normal and overweight individuals) (Nieto et al. 2000). In fact, OSA causes acute nocturnal surges in blood pressure in response to hypoxia-mediated stimulation of the sympathetic nervous system, which may sometime reach to a high level such as 240/120 mm Hg (Somers et al. 1995). Interestingly it has been observed that effective treatment of OSA with continuous positive airway pressure (CPAP) helps decrease blood pressure and sleep

disturbances (Becker et al. 2003). All these studies present compelling pieces of evidence in support of the association between chronic sleep loss and hypertension. The underlying cause, at least in part, may be attributed to notable sympathetic overactivity and also to humoral, neuroendocrine, and metabolic abnormalities.

Many reports show that insomnia is a major factor associated with increased risk and mortality of CVD. It has been observed in some prospective cohort studies that the insomniac patients have 33–45% chances of increased CVD risk and mortality, which may develop within 3 to 20 years (Javaheri and Redline 2017; Sofi et al. 2014). The patients of chronic heart and cardiopulmonary diseases experience poor sleep quality, but at the same time, the chance of mortality significantly increases, if insomnia chronically persists in such patients (Javaheri and Redline 2017; Parthasarathy et al. 2015). Cognitive-behavioral therapy for insomnia (CBT-I) is widely used as sleep management therapy to reduce the risk of mortality in CVD patients (Perlis et al. 2008). The CBT-I includes (1) sleep consolidation (homeostatic sleep drive generation through bedtime management based on actual sleep efficiency), (2) stimulus control (bed and sleep association), (3) sleep hygiene (alteration in a household environment and pre-bedtime ritual), (4) cognitive training (education, identification, and modification in maladaptive beliefs about sleep), and (5) relaxation training (providing exercises training such as breathing exercises and mindfulness meditation) (Perlis et al. 2008). These growing pieces of evidence suggest that persistent insomnia increases the risk of hypertension and heart diseases with or without confounders such as obesity, mood, and stress.

4.3.6 Prolonged Sleep Loss and Alteration in Metabolic Energy Conservation and Cellular Detoxification

One of the essential functions of sleep is to conserve metabolic energy. One would need more energy intake per day without sleep to perform the day-to-day activity. Recently, Jung et al. have quantified energy expenditure during sleep, sleep deprivation, and recovery sleep in humans (Jung et al. 2011). They have observed that energy expenditure was higher during sleep deprivation compared to the corresponding sleep period. Furthermore, they found that energy expenditure was lower during the 8 h recovery sleep after sleep deprivation compared to the corresponding normal sleep period (Jung et al. 2011). Interestingly, their finding suggests that metabolic cost was quite high after missing one-night sleep (Jung et al. 2011). The intriguing question is, how does sleep contribute to saving metabolic energy for our brain and body? The possible explanation could be that the decreased energy consumption during sleep may be the net results due to suppression of metabolically costly physiological processes such as respiration, heart rate, gut motility, and muscular activity (Kumar et al. 1990; Shinar et al. 2006; Trinder et al. 1992). Also, it has been noted that along with the augmented energy expenditure, food intake increases during sleep deprivation. It is primarily because the levels of satiety hormone “leptin” decreases (Mullington et al. 2003) and the levels of hunger hormone “ghrelin” increases (Havel 2001; Schmid et al. 2008) after sleep

deprivation, which may enhance hunger. Thus, sleep loss contributes to increased food intake and energy expenditure by activating cellular metabolic processes.

Several reports suggest that sleep deprivation also caused cellular accumulation of several toxic biomolecules due to increased metabolic activity. Cells primarily derive energy from the tightly controlled biochemical oxidation of substrates such as carbohydrates and fats by increasing cellular metabolic activity. This augmented metabolic strategy to obtain energy in the form of ATP is extremely efficient, but this process does lead to the formation of reactive oxygen species and other free radicals as byproducts. These byproducts cause oxidative damage to the biomolecules, such as DNA and proteins (Spitz et al. 2004). Additionally, reactive oxygen species and free radicals also cause apoptosis (programmed cell death) and/or necrosis (Spitz et al. 2004). A variety of antioxidative enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx) help regulate the level of reactive oxygen species (ROS). With prolonged sleep deprivation in the rats, it was observed that the activities of SOD and GPx significantly decreased in the hippocampus and brainstem, suggesting an alteration in the metabolism of ROS, resulting in oxidative stress (Ramanathan et al. 2002). Not only does sleep deprivation cause increased production of ROS, but it also changes the neuronal membrane properties and causes neuronal death (Biswas et al. 2006; Mallick et al. 1995; Pal et al. 2005). Hence, it seems that sleep downregulates the production of toxic substances such as ROS and free radicals by decreasing cellular metabolic activity and helps guard cellular damage.

Sleep also plays an essential role in toxin or toxic metabolite clearance. The role of sleep in the metabolite clearance can be clearly understood through two different approaches: (1) accumulation and clearance of metabolites during sleep and wakefulness and (2) the influence of metabolites in the modulation of sleep–wakefulness. The metabolites may efficiently be cleared if the interstitial space dimension enlarges periodically. Interestingly, it has been reported that the cortical interstitial volume increases during sleep (Xie et al. 2013). Xie et al. have checked the clearance of a CSF tracer (Texas red-dextran, 3kD) during sleep and wakefulness. They noticed that the tracer clearance was 95% less during wake compared to the sleeping subjects (Xie et al. 2013). Similarly, the clearance of exogenously injected radiolabeled amyloid beta-protein (125I-Aβ1–40) was twice faster in the sleeping animals compared to the wake animals (Xie et al. 2013). The level of endogenous brain's amyloid beta-protein fluctuates across sleep–wakefulness. The level increases during wake and decreases during sleep (Beekly et al. 2007). Also, the level of the Aβ42 protein in the CSF negatively correlates with NREM sleep duration and amount in cognitively normal elderly (Varga et al. 2016). The decreased level of the Aβ42 protein in the CSF during sleep suggests that sleep possibly helps in the clearance of nonessential biomolecules from the CSF and interstitial fluid. It can further be supported with the findings that sleep stimulates the lymphatic system (that increases in interstitial volume) (Mendelsohn and Larrick 2013). All these demonstrate that sleep possibly removes toxic metabolites through convective flow from the brain.

On the other hand, some metabolites can effectively influence sleep–wake behavioral states. For example, a mild increase in the bodily CO_2 level increases sleep,

while a high level of CO_2 increases wakefulness (Fraigne et al. 2008). Interestingly, the breathing rate during NREM sleep remains low, while it increases during REM sleep. Therefore, the increased breathing rate during REM sleep might help in removing a mild increase in the CO_2 level without inducing wakefulness. One of the important functions of REM sleep could be that it possibly acts as a sentinel to help maintain the bodily CO_2 level within physiological limits during sleep (Madan and Jha 2012).

4.4 Conclusion

Sleep plays an indispensable role in keeping our brain and body healthy. The immunity diffuses into the compromised state, and the body becomes weak and susceptible to infections due to a lack of sufficient sleep. There is no doubt that sleep is one of the key components involved with the proper functioning of cognitive, metabolic, and physiological systems. Sleep loss is affecting the health of adults as well as aged people. The brain shrinks, and the body becomes vulnerable to diseases. It affects the brain and neural development in children too. Even though it has so many consequences, it is becoming an epidemic in our modern society. Scientific evidence for implications of sleep loss should be outreached so that ill practices in lifestyle can be renounced.

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Sleep: Neural Optimization as an Ultimate Function for Memory Consolidation

5

Abstract

Many studies support the role of sleep in memory consolidation. The performances improve after sleep as compared to being awake for the same duration in the following night after learning. Besides, sleep-dependent memory consolidation does not seem to depend on specific states of sleep; instead, each stage of sleep contributes differently to the memory consolidation process. The process of memory consolidation involves many pieces of biological machinery, such as activation of second messenger systems, increased expression of memory-associated genes, induction of long-term potentiation and depression, the formation of new spines and new synapses, recruitment of new receptors, and generation of new neurons/circuitries. Most of the memories require the activation of these processes for offline memory consolidation during sleep. It is not known, however, how sleep triggers many types of biological machinery of memory consolidation. There is evidence that supports the role of sleep-related oscillatory waves in determining the timing of neural activity, which can, in turn, trigger and activate all necessary biological machinery essential for memory consolidation. In addition, data suggest that sleep plays a critical role in maintaining the optimal condition of the neural system to begin the processes of memory consolidation. Here, we put forward a "system optimization theory" (SOT), according to which a crucial function of sleep could be the maintenance of optimal neural conditions for the process of memory consolidation to take place. We propose "SOT" in an attempt to answer a very crucial question, "why sleep remains a favored state for memory consolidation?"

Keywords

Adult neurogenesis · Learning · Oscillatory waves · SWA · Synaptic plasticity

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5.1 Introduction

Scientific evidence demonstrates that sleep performs many fundamental functions such as energy restoration, metabolic regulation, thermoregulation, boosting immune system, brain and body detoxification, brain maturation, circuit reorganization, and synaptic optimization. Chronic sleep deficit causes several enduring structural, biochemical, functional, and cognitive alterations, which ultimately damages health and causes early onset of aging. Even individuals suffering from recurring short-term insomnia show difficulties in decision making, problem solving, emotional disturbances, coping with challenges, and so on. Every individual learns several essential skills and gains knowledge and information in day-to-day life for performances, earnings, and survival. In current times of competitive work culture, people of all ages compromise on their sleep quality and quantity. This insufficient sleep induces detrimental effects on an individual's learning and memory.

Many pieces of evidence support the view that sleep facilitates the processes of memory strengthening (Diekelmann and Born 2010; Diekelmann et al. 2009; Madan and Jha 2008; Qureshi et al. 2019; Stickgold 2005; Tripathi and Jha 2019). Sleep helps in memory consolidation at several levels, such as systems level as well as cellular and molecular levels. In one of the early studies, in 1924, Jenkins and Dallenback found that sleep might be helping memory in its stabilization (Jenkins and Dallenbach 1924). They found that the rate of memory forgetting was much slower after sleep than waking (Jenkins and Dallenbach 1924). Since then, the role of sleep in memory consolidation has been investigated extensively, and many studies have shown that the rate of memory recall significantly increases following sleep (Gais and Born 2004a, b). Not only does sleep facilitate the processes of memory consolidation, but it also plays an active role in memory consolidation and helps in long-term retention as well as retrieval of the encoded information (Ellenbogen et al. 2006).

Sleep as a whole or its specific stage might be playing roles in memory consolidation (Kumar and Jha 2017; Qureshi and Jha 2017; Qureshi et al. 2019). For example, declarative memory is associated with NREM sleep (Gais and Born 2004a, b). Memory-associated neuronal activation during memory acquisition in the hippocampus is replayed almost in a similar fashion in the same circuitries during NREM sleep. It is believed that such replay during NREM sleep is crucial for memory consolidation (Pavlides and Winson 1989; Wilson and McNaughton 1994). McNaughton and several other groups have observed replay in the hippocampal during early bouts of NREM sleep after learning the task (Ji and Wilson 2007; Louie and Wilson 2001; Skaggs and McNaughton 1996; Wilson and McNaughton 1994). Reports suggest that the neuronal replay in the hippocampus during NREM sleep helps improve performances; hence, it could be an essential event underlying the process of memory consolidation.

The presentation of learning-associated cues during NREM sleep enhances neuronal replay of the same group of neurons that were active during acquisition, and such targeted reactivation improves performances. For example, in associative learning, two stimuli (auditory or sensory such as olfactory or taste) are presented

together (Chowdhury et al. 2011; Jha et al. 2005a; Qureshi et al. 2019; Tripathi and Jha 2016). If the same stimulus (either auditory or olfactory) is presented again during the subsequent NREM sleep episodes, it robustly enhances memory in subjects compared to those who are not exposed to the same stimulus during NREM sleep (Rasch et al. 2007).

Similar to NREM sleep, REM sleep also plays a significant role in the consolidation of memory traces. It is reasoned that NREM sleep may be playing a role during the initial phase of memory consolidation, whereas REM sleep may be taking part in the memory consolidation at the later stage (Datta 2000; Louie and Wilson 2001). REM sleep may be playing a role in the optimization and reorganization of neuronal circuitries for memory consolidation (Laureys et al. 2001; Peigneux et al. 2001). It is also likely that the neocortical and hippocampal activation during REM sleep may have a role in restrengthening the old week memory and thus facilitating memory recall (Poe et al. 2000).

NREM sleep and REM sleep both play an essential role in memory consolidation, but some questions raise curiosity, such as why does memory consolidation require sleep? What does sleep offer for memory consolidation? When does sleep facilitate memory consolidation: sleep during the day or sleep at night? In this chapter, we have attempted to discuss the answer to such questions and a possible role of sleep in maintaining the neural system at an optimal level, which is required intrinsically for memory consolidation.

5.2 Sleep-Dependent Memory Consolidation and Synaptic Plasticity

5.2.1 The Role of Sleep in Memory Consolidation

A wide range of studies supports the role of sleep in memory consolidation. For example, the improvement in cognitive performances of visual texture discrimination task (Stickgold et al. 2000a), motor adaptation task (Mantua et al. 2016), and motor sequence task (Nettersheim et al. 2015) is benefited by sleep in humans. Performance becomes unquestionably better during post-training undisturbed sleep in the subsequent night compared to being awake for the same duration in the night after learning (Stickgold 2005; Stickgold et al. 2000a, b). Specific sleep states help in the consolidation of certain memories. Improvement of visual discrimination tasks significantly correlated with the NREM and REM sleep amount (Stickgold 2005), while the improvement of motor adaptation and sequence tasks positively correlated with the NREM sleep and its local component (Huber et al. 2004; Stickgold 2005). Likewise, NREM sleep (out of total sleep time) proportionally increased, and REM sleep decreased after learning associated with fearful memories (Jha et al. 2005a; Kumar and Jha 2012, 2017; Qureshi and Jha 2017; Qureshi et al. 2019). Therefore, for these tasks, sleep-dependent memory consolidation does not seem to depend on specific states of sleep, but each stage of sleep seems to contribute differently to these processes.

Sleep also plays an essential role in the consolidation of implicit memory, particularly the associative memory. Studies from several laboratories have shown that the total sleep deprivation impaired the consolidation of fear-conditioned as well as appetitive-conditioned memories (Graves et al. 2003; Kumar and Jha 2012; Tripathi and Jha 2016, 2019; Tripathi et al. 2018, 2020). Short-term sleep deprivation alters the consolidation of contextual as well as cued fear memory in rats and mice (Graves et al. 2003; Kumar and Jha 2012; Qureshi and Jha 2017; Qureshi et al. 2019). Earlier it was reported that short-term sleep deprivation might alter the consolidation of contextual fear memory but not cued fear memory (Graves et al. 2003). It was presumed at one point in time that the hippocampal-dependent memory is more sensitive to sleep deprivation (Havekes and Abel 2017; Kreutzmann et al. 2015). Nevertheless, it now appears to a broader extent that sleep loss is detrimental to a variety of learning tasks.

On the one hand, sleep loss alters memory consolidation, but on the other hand, memory consolidation also requires augmented sleep. The Bayesian probabilistic model is widely used in the cognitive field to understand the probability of a factor in influencing the cognition ability. Using the "Bayes rule", we have demonstrated that within sleep, the consolidation of fearful memory requires augmented NREM sleep. We applied the Bayes rule to predict if there is (a) high probability for the expression of augmented NREM sleep after the consolidation of cued fear memory and (b) low probability for the expression of augmented NREM sleep after a cued fear memory was impaired. We observed that the probability of NREM sleep augmentation increased significantly after fear conditioning, and the probability of increased NREM sleep was very low when the memory was impaired (Qureshi et al. 2019). Another essential observation is that REM sleep decreases significantly after fear conditioning (Kumar and Jha 2012, 2017; Qureshi and Jha 2017; Qureshi et al. 2019). REM sleep is considered to be a sensitive index of fear conditioning (Jha et al. 2005a). It decreases significantly after cued fear conditioning (Kumar and Jha 2012, 2017), passive avoidance task (Mavanji and Datta 2003; Mavanji et al. 2004), and contextual fear conditioning (Qureshi and Jha 2017; Qureshi et al. 2019). REM sleep decreased only in the fear-conditioned memory-consolidated group; it did not decrease in the fear-conditioned memory-impaired group (Kumar and Jha 2017; Qureshi and Jha 2017). Furthermore, REM sleep increases with fearful memory extinction but decreases after fear conditioning (Wellman et al. 2008). REM sleep decreases after extensive fear training using inescapable shock but increases in animals trained with less extensive fear training such as escapable shock (Yang et al. 2011). Animals trained with inescapable shock demonstrate stronger fear memory trace during testing than animals trained with escapable shock (Mineka et al. 1984). The consolidation of fear memory may possibly require NREM sleep only and not REM sleep. It appears that the consolidation of fearful memory is intricately interwoven with the pattern of sleep manifestation.

5.2.2 The Role of Sleep in the Regulation of Epigenetic and Second Messenger Machinery for Memory Consolidation

How sleep benefits consolidation of fear memory is not known. However, some reports suggest that several factors may cause sleep-deprivation-mediated cognitive deficits. For example, sleep deprivation alters signaling and activity level of mTORC1, cAMP/PKA, PDE4, GluR1 dephosphorylation (which limits receptor insertion into the synaptic membrane), and BDNF and pCREB in the hippocampus, which are mainly required for the consolidation of contextual fear memory (Hagewoud et al. 2010; Havekes et al. 2007; Nami et al. 2014; Vecsey et al. 2009). One of the structural-protein-related genes, "formin2" in the hippocampus, also plays a vital role in the regulation of this sleep-dependent consolidation of contextual fear memory (Qureshi and Jha 2014). The administration of histone deacetylase (HDAC) inhibitors in the aged animals restored the altered expression of the learning-mediated gene and memory function (Peleg et al. 2010). Similarly, microinjection of a HDAC inhibitor, suberoylanilide hydroxamic acid "SAHA" in the hippocampus, rescued sleep-deprivation-mediated learning deficit. The SAHA-administered sleep-deprived animals demonstrated robust learning behavior compared to the drug-nonadministered animals (Qureshi et al. 2019). These results suggest that sleep might be playing a regulatory role at the epigenetic as well as the second messenger levels for the expression of memory-associated genes.

5.2.3 The Role of Sleep in Neuronal Proliferation

Hippocampal-dependent learning, such as the appetitive trace conditioning, increases cell proliferation and neurogenesis in the hippocampus. An increase in cell proliferation and adult neurogenesis seems to be exclusively associated with the hippocampal-dependent task (Fig. 5.1) (Tripathi et al. 2020). The non-hippocampal-dependent task does not increase adult neurogenesis in the DG area of the hippocampus (Tripathi et al. 2020). The expression of several proteins and their phosphorylation such as Arc, Erk-1, Erk-2, and CREB increases in the dorsal part of the hippocampus, which could be involved in memory consolidation as well as memory-associated increase in cell proliferation (Tripathi et al. 2020). Interestingly, we have observed that the expression of pErk1, pErk2, and pCREB proteins increased in the dorsal hippocampus after learning the hippocampal-dependent "appetitive trace-conditioning" task and the expression of pErk1, pErk2, and pCREB proteins increased in the ventral hippocampus after learning the hippocampal-independent "appetitive delay-conditioning" task (Tripathi et al. 2020). Not only does long-term total sleep deprivation reduce learning-induced cell proliferation and adult neurogenesis in the hippocampus, but it also significantly alters the survival of these newly generated neurons in the hippocampus (unpublished data from our lab) (Meerlo et al. 2009).

Sleep deprivation also alters the learning-induced changes in the expression levels of Arc, Erk-1, Erk-2, and CREB proteins in the hippocampus (Havekes

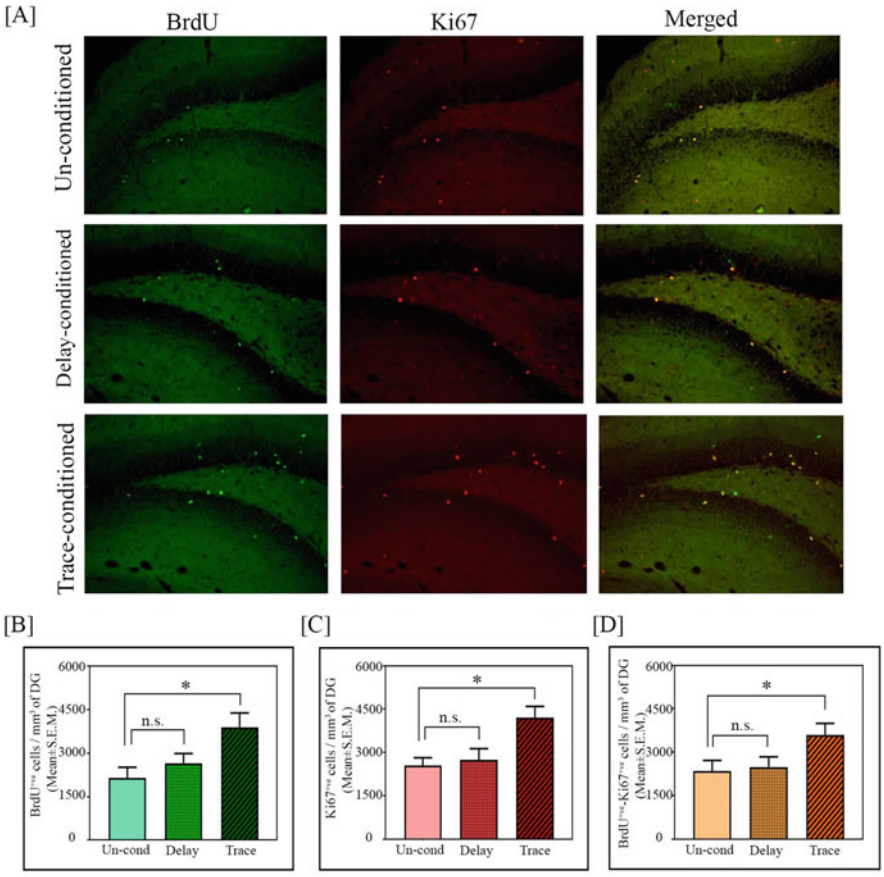

Fig. 5.1 The changes in the number of BrdU+ve & Ki67+ve double-labeled cells in the DG area in the delay- and trace-conditioned animals. (**a**) Photomicrographs of the DG area showing BrdU+ve, Ki67+ve, and BrdU+ve & Ki67+ve double-labeled cells in unconditioned, delay-conditioned, and trace-conditioned animals (×10 magnification). Green dots show BrdU+ve, red dots show Ki67 +ve, and yellow and orange dots show BrdU+ve and Ki67+ve double-labeled cells in the DG area of the hippocampus. Bar graphs showing the number of (**b**) BrdU+ve cells/mm^3 of DG, (**c**) Ki67+ve cells/mm^3 of DG, and (**d**) BrdU+ve & Ki67+ve double-labeled cells/mm^3 of DG in unconditioned, delay-conditioned, and trace-conditioned animals. There was a significant increase in the number of BrdU+ve cells (*$p < 0.05$; $F(2, 8) = 5.67$), Ki67+ve cells (*$p < 0.05$; $F(2, 8) = 6.58$), and BrdU +ve and Ki67+ve double-labeled cells (*$p < 0.05$; $F(2, 8) = 7.73$) in the trace-conditioned animals (one-way ANOVA followed by Tukey post-hoc), compared to the unconditioned control animals. The numbers of BrdU+ve cells, Ki67+ve cells, and BrdU+ve and Ki67+ve double-labeled cells in the delay-conditioned animals were comparable to the unconditioned control animals. [Figure taken from (Tripathi et al. 2020)]

et al. 2012). The learning-induced proliferative cells transform into neurons and become a part of hippocampal neuronal circuitries over time (Fig. 5.2). These newly generated and well-developed neurons of the circuitries actively help in memory

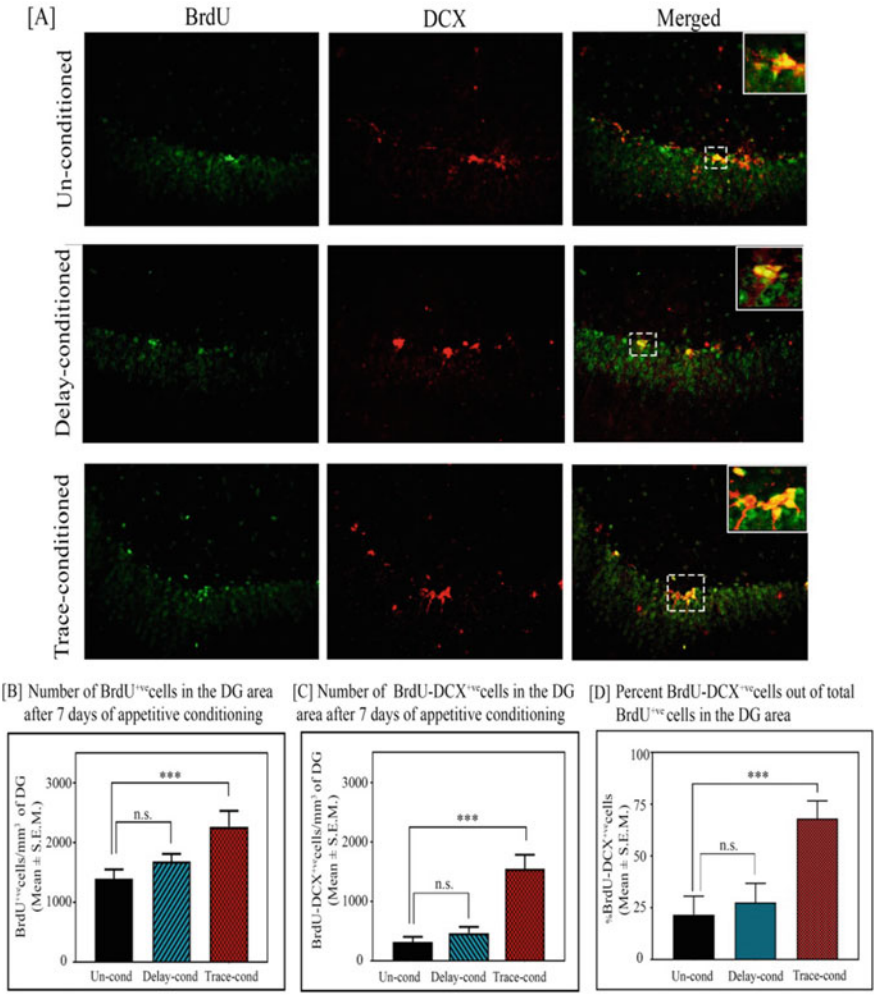

Fig. 5.2 The number of newly proliferated cells progressed toward the neuronal lineage in the dentate gyrus of the hippocampus 7 days after appetitive delay and trace conditioning. (**a**) Photomicrographs (×20 magnification) showing BrdU+ve, DCX+ve, and BrdU+ve & DCX+ve double-labeled cells in the dentate gyrus of the hippocampus in the unconditioned, delay-conditioned, and trace-conditioned animals. Green dots show the BrdU+ve, red dots show DCX +ve, and yellow and orange dots show BrdU+ve and DCX+ve double-labeled cells. Magnified views of BrdU+ve, DCX+ve, and BrdU+ve and DCX+ve cells are shown in the inset. The average number of (**b**) BrdU+ve cells/mm^3 of DG and (**c**) double-labeled BrdU+ve and DCX+ve cells/mm^3 of DG in the unconditioned, delay-conditioned, and trace-conditioned animals. The BrdU+ve cells significantly increased in the trace-conditioned animals (***$p < 0.001$), compared to the unconditioned control animals. The BrdU+ve cells in the delay-conditioned animals were comparable to the unconditioned control animals. The number of BrdU+ve cells in delay-conditioned animals was comparable to unconditioned control animals. Similarly, the average number of BrdU+ve and DCX +ve double-labeled cells was significantly more in trace-conditioned animals compared to unconditioned animals (***$p < 0.001$). (**d**) Out of total BrdU+ve cells, 67.9% significantly progressed toward the neuronal lineage in the trace-conditioned animals (***$p < 0.001$), whereas the

retrieval of the same task that had triggered their proliferation (Deng et al. 2010). These findings demonstrate that sleep helps in learning-induced cell proliferation and neurogenesis in the hippocampus, possibly by actively modulating the expression level of Arc, Erk-1, Erk-2, and CREB proteins. Furthermore, the number of proliferating cells in the hippocampus correlated significantly positively with the extent of learning, suggesting that learning-induced recruitment of new neuronal cells may help in better estimation of their surroundings and memory retrieval (Tripathi et al. 2020). These studies demonstrate that sleep helps in optimizing the neuronal population in the hippocampal network for long-term memory preservation.

5.2.4 The Role of Sleep in Neural Circuit Reorganization

Sleep also plays an essential role in the reorganization of neural circuitries in the brain. In the developing brain, synaptic connectivity in the visual cortex exhibits dynamic plasticity, and sensory stimuli guide the formation of new connections, as well as retraction of old connections (Hubel and Wiesel 1970). For example, occluding the vision briefly in one eye causes a reduction in the neural responses from the occluded eye and a corresponding increase in the neural responses from the nonoccluded eye. This phenomenon is called "ocular dominance plasticity," and the sensitivity of such neural circuit reorganization is high in juvenile animals during a critical period in early life (Hubel and Wiesel 1970). The changes in neural weightage can be potentiated by sleep, and total sleep deprivation during the period of synaptic potentiation impairs the mechanism of circuit reorganization (Frank et al. 2001). Interestingly, the remodeling neurons exhibit significantly enhanced activity in the first 2–4 h of subsequent NREM and REM sleep. The reversible silencing of the postsynaptic activity in the visual cortex during sleep blocks the circuit reorganization (Jha et al. 2005b). Also, the activation of glutamatergic NMDAR receptors and several protein-kinase activities during sleep play an essential role in the potentiation of synaptic strengthening in the visual cortex (Aton et al. 2009). The blockage in the normal vision of one eye in the kittens, along with REM sleep deprivation, for 2 weeks, causes anatomical and functional abnormalities of a higher magnitude in the lateral geniculate nucleus compared to the non-sleep-deprived animals (Marks et al. 1995). Also, occlusion of the ponto-geniculo-occipital wave, a REM sleep phasic activity, induced similar results in the LGN (Shaffery et al. 1999). REM sleep deprivation not only delays the development of synaptic plasticity in the LGN but also alters the maturational reduction of long-term potentiation (LTP) in the visual cortex of the juvenile rats (Marks et al. 1995; Shaffery et al. 2002). The

Fig. 5.2 (continued) progression of dividing cells in the delay-conditioned animals toward neuronal lineage was comparable to that of in the unconditioned animals. [Figure taken from (Tripathi et al. 2020)]

optimized neural circuitries are essential for their functional maturation, and sleep seems to play a crucial role in optimizing the neural systems.

5.2.5 The Role of Sleep in Memory-Linked Neuronal Replay

The neural reactivation/replay during the subsequent post-learning sleep in a similar spatiotemporal pattern remains one of the surprising events in sleep and cognitive fields (Euston et al. 2007; Ji and Wilson 2007; Lansink et al. 2008; Nadasdy et al. 1999; Pavlides and Winson 1989; Wilson and McNaughton 1994). The neuronal replay during post-learning sleep is usually observed during the first few hours of NREM sleep but is rarely seen in REM sleep (Louie and Wilson 2001; Poe et al. 2000). The neurons of zebra finch's motor cortex exhibit very similar neural activity patterns during sleep as it is during daytime singing (Dave and Margoliash 2000). The neural song-replay during sleep is believed to be involved in creating a repeated opportunity for the performance-linked rehearsal and to reshape previously learned motor skills (Deregnaucourt et al. 2005). Similarly, the responsiveness of the auditory tone associated with tone-conditioned memory robustly increases in the hippocampus, and the auditory thalamus exclusively during post-conditioning sleep. It suggests that sleep might be keeping these neurons in an optimized condition for their better performances and memory update. In humans too, learning induces sleep-dependent signs of reactivation in several brain regions. New memories with odor were formed as context, and repeated odor reexposure during NREM sleep, as task replay, improved memory retention (Rasch et al. 2007). Furthermore, reactivation also has implications in memory transfer and memory updates. It has been reported that sleep helps in strengthening the inter-hippocampal functional connectivity for memory transfer between the hippocampus and the mPFC (Gais et al. 2007; Takashima et al. 2006). This suggests that reactivated neural circuitries could be a part of offline memory processing, and this could be primarily for two reasons: (a) neural recapitulation for memory optimization and (b) memory transfer and memory update for long-term retrieval.

5.3 Why Does Memory Consolidation Require Sleep?

Many biological processes work in concert, but almost independently, the processes of memory consolidation are contingent on sleep. Memory consolidation involves many processes such as activation of second messengers, the expression of memory-associated genes, synapse perforation, receptor upscaling, the formation of new spines or synapses, induction of long-term potentiation and depression, generation of new neurons/circuitries, and neuronal replay. Almost all memories require the activation of these processes for online as well as offline memory processing. More so, the activation for offline processing occurs during sleep. It is intriguing to ask who triggers these machineries for memory consolidation during sleep.

The role of endogenous oscillatory waves during sleep could be the answer to the above question. The oscillatory waves can modulate the precise occurrence and timing of neuronal activity in response to excitatory postsynaptic potentials (Desmaisons et al. 1999), which is induced in the neural circuitries associated with memory. Voltage-gated ionic conductance plays an essential role in synaptic integration and transformation into action potential (Hille 1992). It addition, it is involved in the generation of several neuronal nonlinear functions (Haag and Borst 1996; Stuart and Sakmann 1995), which allows neurons to precisely integrate several synaptic events, such as coincidence detection across time (Larkum et al. 1999). The interaction between oscillatory patterns and synaptic inputs, such as coincidence detection, is the only effective means to synchronize neuronal action potential with oscillatory waves (Connors and Amitai 1997; Ritz and Sejnowski 1997). These findings suggest that oscillatory waves can play an essential role in synaptic event reactivation for memory consolidation during sleep.

A local increase of slow-wave activity during sleep has been observed explicitly in learning-associated brain areas, and such augmentation in slow-wave activity significantly correlated with improved performance (Figs. 5.3 and 5.4). On the other hand, slow-wave activity significantly decreased during sleep in learning-associated brain regions, if the learning was impaired (Huber et al. 2006). Interestingly, EEG slow-wave activity also increases during learning while asleep (Arzi et al. 2012). Using partial-reinforcement trace-conditioning paradigm, pleasant and unpleasant odors paired with different tones were presented during sleep. It was found that (a) sleeping subjects learned novel associations between tones and odors and (b) most importantly, the power of SWA and sigma waves significantly increased at a post-tone period during sleep after learning (Arzi et al. 2012). Similar changes occur in SWA and sigma waves during NREM sleep after learning the appetitive task (Tripathi et al. 2018). These results demonstrate that learning may require different cortical waves, which are prevalent only during sleep.

Why learning needs increased cortical waves in the SWA, theta, and sigma range is not precisely known. Interestingly, the enhanced cortical oscillations of SWA and spindle-like potential by either magnetic stimulation or pharmacologic interventions after learning help potentiate memory consolidation. Using an intermittent transcranial direct-current stimulation (0.75 Hz) technique, Marshal et al. have found an increase in the EEG power in the slow oscillation band (<1 Hz) during the stimulation-free intervals (Marshall et al. 2006). The increase was remarkably associated with enhanced memory retention (Marshall et al. 2006). On the other hand, some drugs such as gaboxadol and tiagabine induce restorative sleep along with a robust increase in SWA during NREM sleep (Walsh et al. 2006, 2008). As compared to the control group, the drug-treated groups exhibited better performances in the psychomotor vigilance test, and Wisconsin card-sorting task after sleep restriction (Walsh et al. 2006, 2008). These further demonstrate that slow-wave oscillation in the SWA range during NREM sleep may be one of the underlying factors essentially required for memory consolidation.

A successful memory encoding also accompanies an increase in theta power, which remains prevalent during REM sleep (Berry and Thompson 1978; Hutchison

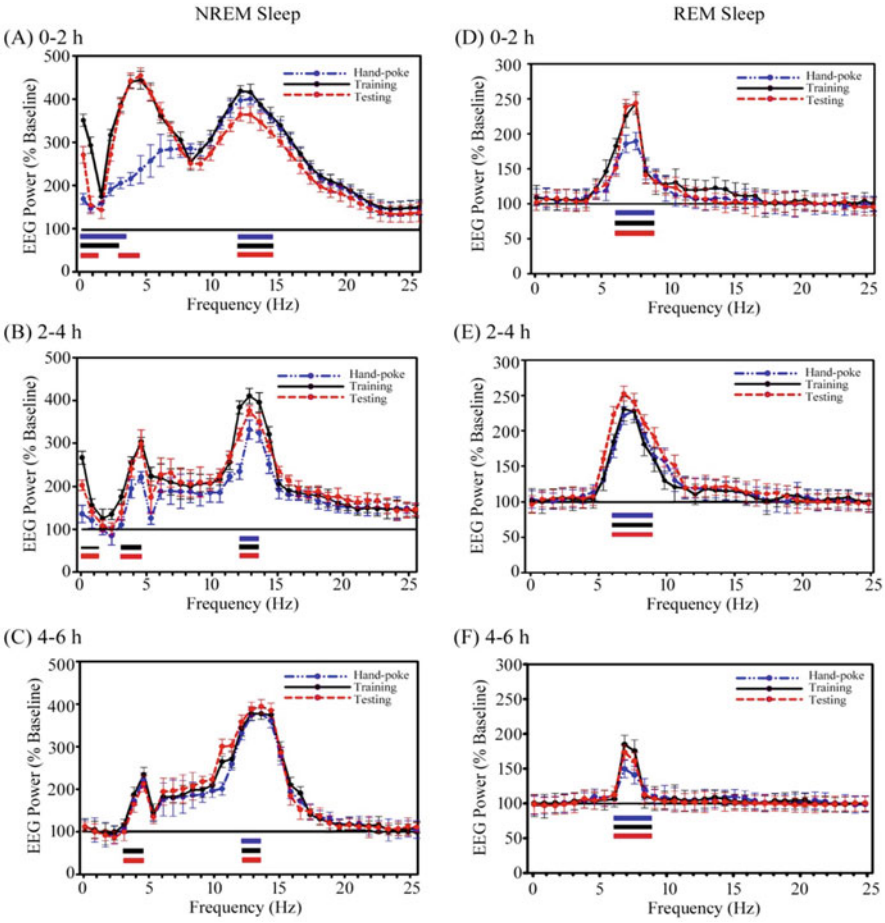

Fig. 5.3 The cortical EEG's SWA and sigma waves (spindles) recorded from the parietal cortices during NREM sleep and theta waves during REM sleep significantly increased on the training and testing days. (**a**) During NREM sleep, SWA significantly increased in the 0.1–3.75 Hz range on the hand-poke training day, the 0.1–3.0 Hz range on the training, and the 0.1–1.5 Hz and 3–4.5 Hz range on the testing days during the 0–2 h period. EEG power in sigma range (12–14.25 Hz) during NREM sleep also significantly increased on the hand-poke training, appetitive-conditioned training, and testing days during 0–2 h compared to the baseline day. (**b**) SWA significantly increased in the 0.1–1.5 Hz and 3–4.5 Hz range during 2–4 h after appetitive-conditioned training and testing. Sigma waves also remained significantly augmented in 12–13.5 Hz during 2–4 h after hand-poke training and appetitive-conditioned training and testing. (**c**) Interestingly, SWA remained significantly increased in the high-frequency range (3.0–4.5 Hz) during 4–6 h after appetitive-conditioned training and testing. The power of EEG's sigma waves remained consistently augmented in the 12–13.5 Hz frequency range during the 4–6 h period after hand-poke training and appetitive-conditioned training and testing. Theta wave (6–9 Hz) during REM sleep remained significantly increased during the (**d**) 0–2 h period, (**e**) 2–4 h period, and (**f**) 4–6 h period after hand-poke training and appetitive-conditioned training and testing. (Taken from: Tripathi et al. 2018)

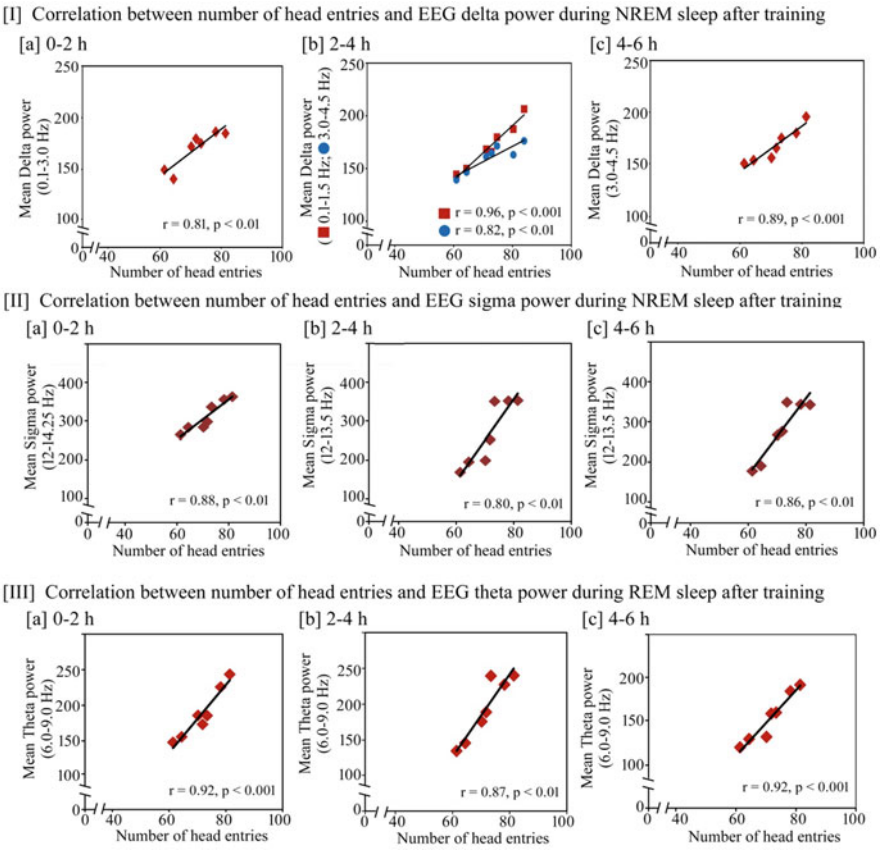

Fig. 5.4 Pearson correlation between performance (number of head entries) and percentage change in cortical oscillatory waves during NREM and REM sleep on the training day. On the training day, (**I**) the number of head entries significantly positively correlated with the increased power of SWA in the range of 0.1–3 Hz ($r = 0.81$; $p < 0.01$) at 0–2 h (*a*), 0.1–1.5 Hz ($r = 0.96$; $p < 0.001$) and 3–4.5 Hz ($r = 0.82$; $p < 0.01$) at 2–4 h (*b*), and 3–4.5 Hz ($r = 0.89$; $p < 0.001$) at 4–6 h (*c*); (**II**) the increased power in sigma waves during NREM sleep also significantly positively correlated with performance in the range of 12–14.25 Hz at 0–2 h ($r = 0.88$; $p < 0.01$) (*a*) and in the range of 12–13.5 Hz at 2–4 h ($r = 0.80$; $p < 0.01$) and 4–6 h ($r = 0.86$; $p < 0.01$) (*b* and *c*); (**III**) Theta power during REM sleep in the range of 6–9 Hz also significantly positively correlated with performance during 0–2 h ($r = 0.92$; $p < 0.001$), 2–4 h ($r = 0.87$; $p < 0.01$), and 4–6 h ($r = 0.92$; $p < 0.001$) (*a*–*c*). (Taken from: Tripathi et al. 2019)

and Rathore 2015; Lega et al. 2012). The hippocampal theta oscillation is involved in the formation of episodic memories, emotional memories, and fear memories (Hutchison and Rathore 2015; Lega et al. 2012; Popa et al. 2010). It has been found that theta activity is synchronized in the amygdala–hippocampal network during the tone presentation after fear conditioning (Seidenbecher et al. 2003), and such action has an affirmative role in the consolidation of fear memories (Pape et al. 2005). On the other hand, if theta oscillation is interrupted/eliminated either through

pharmacological interventions or through the medial septal nucleus lesioning, memory consolidation was impaired (Boyce et al. 2016; Givens and Olton 1995; Winson 1978). Also, animals learn faster if they exhibit EEG hippocampal waves predominantly in the theta range before learning compared to animals exhibiting waves in a higher frequency (8–22 Hz) range (Seager et al. 2002). These reports suggest that theta waves may be playing a causal role in memory processing, and theta waves remain more pronounced during REM sleep.

The cortical sigma waves, the cortical and amygdalar SWA waves during NREM sleep, and cortical and amygdalar theta waves during REM sleep increased significantly after learning (Tripathi et al. 2018). The slow and fast oscillatory waves have a role in orchestrating neuronal plasticity and neuronal connections not only during sleep in adults but during development as well (Del Rio-Bermudez and Blumberg 2018; Del Rio-Bermudez et al. 2017; Kurth et al. 2017; Lindemann et al. 2016). The slow and fast oscillatory waves remain synchronized over a large part of the cortex during NREM sleep, and such long-range network synchronization possibly provides a temporal window for processing and strengthening memory (Aton et al. 2009; Chauvette et al. 2012). Theta waves also exhibit a synchronized pattern in the amygdalocortical circuitries, which play a crucial role in potentiating tone-induced fear memory (Popa et al. 2010).

The change in the oscillatory waves in different frequency ranges could be attributed to either (a) the nature of memory (explicit/implicit memory) or (b) memory load. An increase in the power of 3-Hz slow oscillatory waves predicts the successful encoding of episodic memory (Lega et al. 2012). Furthermore, different memory load may influence oscillatory waves in different frequency ranges (van Vugt et al. 2010). The endogenous oscillatory waves during sleep act like a reinforcer for activating memory processing. For this reason, sleep may be the favored state for memory consolidation.

5.4 Memory Consolidation: The Current Concepts

It is now widely believed that memory consolidation during sleep can induce memory strengthening and qualitative changes in memory representations. Memory consolidation occurs in two stages: (a) acquisition and consolidation of new memories initially in primary brain areas such as the hippocampus and amygdala and (b) a gradual transfer from the primary to the secondary long-term storage areas such as the neocortex. Sleep plays an important role in memory storage and offline mode of brain processing in both (1) memory consolidation in the primary area and (2) memory redistribution in other neuronal networks. Memory acquisition and memory recall always occur when someone is awake, but memory consolidation, which involves neural circuit stabilization and strengthening, occurs during sleep. The older concepts delineate the role of NREM and REM sleep in different memory systems, but the current concept takes an all-inclusive view of the role of sleep in memory consolidation.

Initially, acquired memory passes through a long trajectory before it becomes stable and acquires resistance from labilization. As has been proposed earlier, consolidation of declarative memory undergoes through three sequential neurobiological courses: (a) activity-dependent reverberation, (b) induction of plasticity engram, and (c) initiation of wiring engram (Langille 2019). The newly acquired memory remains transiently weak, but its stabilization depends on the strengths of neural circuit reverberation (Langille 2019). The strength of reverberation in neural circuits helps the information to undergo into the second course, that is, induction of plasticity engram. The plasticity engram is initiated in the primary brain areas such as the hippocampus, where the circuits undergo a rapid and resistive interference changes for temporary but reliable storage of information (Langille 2019). The primary brain areas, such as the hippocampus, can encode information rapidly by inducing plasticity engram as it has all possible systems to communicate within and outside the circuitries for reliable memory processing (Langille 2019). After this time point, the wiring engram is initiated, which primarily includes changes in the morphology and number of synapses in the dynamic circuitries. The contextual reminders of previously consolidated memories can reactivate plasticity engram or wiring engram, and memory can be updated with new information through reconsolidation, which can influence both plasticity engram and wiring engram. Sleep not only plays an important role in memory reconsolidation but also contributes to updating the previously consolidated trace with new information (Bryant et al. 2019).

5.4.1 The Systems-Level Consolidation

This hypothesis assumes that memory consolidation begins with the repeated reactivation of newly encoded memory traces during sleep (Born and Wilhelm 2012). The reactivation mediates the redistribution of the transiently stored traces in the primary brain areas, such as the hippocampus, to the long-term storage sites, such as the neocortex. In the neocortex, the information integrates with either preexisting stable memories or forms new engram. This hypothesis also presumes that the waking brain encodes the initial events parallelly in the primary as well as the secondary brain areas such as in the hippocampal and neocortical networks. The new representation associated with the existing memory probably again reactivates the circuitries and simultaneously primes to integrate the new memories into preexisting networks of old memories. The hypothesis proposes that the reactivation and redistribution of information during sleep occurs through the cortico-hippocampal dialogue, which essentially remains under the feed-forward influence of the slow oscillatory waves during sleep (Born and Wilhelm 2012). The hypothesis highlights three points: (1) memory reactivation during sleep is mainly for consolidation, (2) selectiveness in the consolidation process, as every memory is not enhanced, and (3) memories undergo a qualitative change when transferred to the secondary brain areas for the long-term storage.

5.4.2 The Synaptic Homeostasis Hypothesis (SHY)

This hypothesis assumes that the synaptic strengths and numbers increase after waking experiences and sleep downscales the enhanced synaptic strengths and numbers. This hypothesis primarily highlights the mechanism of synaptic homeostasis (Tononi and Cirelli 2020). The SHY proposes that sleep essentially helps in maintaining the synaptic strength within a limit. Learning during wakefulness causes a net increase in synaptic strength through the mechanism of synaptic potentiation. The strong synapses are metabolically more demanding and require more energy and nutrients. At the same time, these synapses may be more sensitive to saturation and essentially may require synaptic renormalization. As per the hypothesis, sleep could be an ideal state for synaptic renormalization, as the brain remains largely disconnected from the environment, and sleep can downscale the activated synapses through offline processing. It has been categorically pointed out as per the SHY that sleep pays the price of waking. In addition, this hypothesis explains how sleep plays a role in preparing the system for the next learning but not in memory consolidation.

5.4.3 The System Optimization Theory (SOT)

We have discussed in this chapter as well as elsewhere in this book and have given convincing evidence in support of the view that sleep plays an essential role in the optimization of the neural system. We have discussed above how and why sleep is a favored state for memory consolidation. The purpose of sleep in memory consolidation has been demonstrated primarily through sleep deprivation. Most of the machinery involved in memory consolidation, such as the second messenger system, the expression of memory-associated genes, synapse perforation, receptor upscaling, induction of long-term potentiation and depression, and generation of new neurons/circuitries, are normally optimally activated and expressed (Mir et al. 2019; Qureshi et al. 2019; Tripathi and Jha 2019). Several reports have demonstrated that induction of LTP, gene expression, phosphorylation of kinases, neurogenesis, and so on after learning remained activated or expressed suboptimally after sleep deprivation (Mir et al. 2019; Qureshi et al. 2019; Tripathi and Jha 2019). The expression of all the above outcome measures after sleep deprivation is very close to a level that generally remains available to neural systems without learning (Mir et al. 2019; Qureshi et al. 2019; Tripathi and Jha 2019). Therefore, it appears that sufficient sleep after learning provides optimal conditions for the neural system to begin the processes of memory consolidation. Second, why neuronal replay occurs during post-learning sleep in a manner similar to wake? The only plausible explanation, as we have discussed above, is to rehearse (Deregnaucourt et al. 2005). The thumb rule for better performance is an optimal rehearsal, and it can only be achieved through a neural replay with a pattern similar to wakefulness. Third, the optimal increase in the power/amplitude of oscillatory waves during post-learning sleep potentiates the neuronal dialogue between networks, which possibly helps in memory transfer (Tripathi et al.

2018). Fourth, the repeated neuronal replay during sleep, time and again, helps in memory update. The optimal scanning for memory updating is also an essential feature of sleep, or else memory can relinquish its specificity and can undergo either for memory generalization or memory labilization (Bryant et al. 2019). Fifth, as per the standard rule of Hebbian plasticity, the neural networks with coincident events would fire together to enhance their connectivity, whereas the synapses with nonpaired activity will be disconnected. The numbers of synapses increase tremendously during post-learning NREM sleep (Yang et al. 2014). As a consequence, the net synaptic weight and the firing rate increase. It has been argued that sleep promotes synapse formation and also helps in preserving the selected dendritic branches for long-term memory storage (Yang et al. 2014). These findings suggest that sleep promotes Hebbian plasticity and maintains the optimal balance in the number of paired synapses.

Here, we propose the concept of "system optimization theory" (SOT) for the role of sleep in memory consolidation. Our theory SOT explains that sufficient sleep possibly maintains optimal neural conditions to begin the processes of memory consolidation. Nevertheless, sleep deficit might cause the breakdown of the coordination within the system so that it can no longer be maintained at the optimal level, an essential requirement for memory consolidation.

5.5 Conclusion

The role of sleep in memory consolidation seems to be unquestionable, but it is yet not clear how sleep facilitates memory consolidation. The process of memory consolidation involves many biological machineries, such as activation of second messenger systems, increased expression of memory-associated genes, induction of long-term potentiation and depression, the formation of new spines and new synapses, recruitment of new receptors, and generation of new neurons/circuitries. Most of the memories require the activation of these processes for offline memory consolidation during sleep. However, it is intriguing to ask who triggers these machineries during sleep for memory consolidation. Sleep has one remarkable characteristic: the sleep-related oscillatory waves, which may have the potency to determine the timing of neural activity. It can thus modulate or trigger all necessary biological machinery essential for memory consolidation. Besides, many pieces of evidence support our "system optimization theory" (SOT) according to which sleep possibly maintains the optimal neural conditions for the process of memory consolidation to take place.

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Sleep: Disorders and Clinical Implications

6

Abstract

When an individual fails to fulfill the sleep demand, sleep debt starts accumulating. Sleep deficit for an extended period may cause severe complications such as excessive daytime sleepiness, mood swing, fatigue, irritability, anxiety, depression, inability to concentrate or a "fuzzy" head, lack of motivation, clumsiness, forgetfulness, and learning deficit. It may also cause frequent illness, obesity, diabetes, hypertension, and other medical conditions. Therefore, everyone must have an optimal amount of sleep every night. National Sleep Foundation (USA) has proposed the sleep range as follows: in newborns (0–3 months), 14–17 h; infants (4–11 months), 12–15 h; toddlers (1–2 years), 11–14 h; preschoolers (3–5), 10–13 h; school-aged children (6–13), 9–11 h; teenagers (14–17), 8–10 h; younger adults (18–25) and adults (26–64), 7–9 h; and older adults (65+), 7–8 h at every night. An individual may be sleep deprived if he or she fails to attain the minimum daily recommended time in sleep. Sleep deprivation could be intentional or unintentional. Teenagers and young adults may most likely be intentionally sleep deprived. Persons may, however, not get proper sleep unintentionally because of their profession and obligations. Moreover, consistently being late in going to bed, frequent arousals, or early awakening may also contribute to sleep deprivation. The medical problems such as depression, obstructive sleep apnea, hormone imbalances, and other chronic illnesses may also be the reasons for sleep deprivation. There is no substitute for restorative sleep, but some measures may prevent the implications of sleep loss. Therefore, a certain amount of attention is necessarily required to understand the clinical consequences and prevention from chronic sleep debt. Here, we have reviewed the clinical implications of sleep deprivation and other sleep disorders with their diagnostic features.

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Keywords

Insomnia · Narcolepsy · Parasomnia · RLS · Sleep apnea · Sleep-related eating disorder

6.1 Introduction

In the current scenario, the loss of sleep is a common problem across the world. Many individuals are affected primarily because of their modern lifestyle. Sleep is a demand of our body, and its loss only occurs when the individual forces to be awake and entirely evades to compensate. When the individual fails to fulfill the sleep demand, sleep debt starts accumulating. Although sporadic sleep disruption could be no more than a nuisance, chronic sleep deficit induces severe complications. The main symptoms are excessive daytime sleepiness, yawning, moodiness, fatigue, irritability, depressed mood, difficulty in learning, forgetfulness, inability to concentrate or a "fuzzy" head, lack of motivation, clumsiness, increased appetite and carbohydrate cravings, reduced sex drive, and so on. It may also cause frequent illness, obesity, diabetes, and hypertension, all these together leading to poor life quality. Also, it could be a symptom of an undetected medical condition.

It is essential to understand how much time one should spend in sleep daily. The "National Sleep Foundation" (NSF), USA, organized an expert committee meeting in 2015 and recommended a minimum daily sleep time in newborns, children, and young and old adults after lots of deliberations (Hirshkowitz et al. 2015). The panel revised the earlier recommendations and has proposed new guidelines for sleep ranges (Hirshkowitz et al. 2015). They proposed the sleep range for each age group as follows: (a) newborns (0–3 months), 14–17 h each day (previously it was 12–18); (b) infants (4–11 months), 12–15 h (previously it was 14–15); (c) toddlers (1–2 years), 11–14 h (previously it was 12–14); (d) preschoolers (3–5), 10–13 h (previously it was 11–13); (e) school-aged children (6–13), 9–11 h (previously it was 10–11); (f) teenagers (14–17), 8–10 h (previously it was 8.5–9.5); (g) younger adults (18–25), 7–9 h (new age category was proposed); (h) adults (26–64): 7–9 h; and (i) older adults (65+), 7–8 h (new age category). The NSF provided these scientifically grounded guidelines on the amount of sleep one may require each night to maintain growth in children and health, cognition, and mental faculties in all age groups.

An individual may be sleep deprived if he or she fails to attain the minimum daily recommended time in sleep. Sleep deprivation could be intentional or unintentional. Teenagers and young adults may most likely be intentionally sleep deprived (Buxton et al. 2015; Hershner 2015). Some people, however, unintentionally may not get proper sleep because of their profession and obligations (Buxton et al. 2015; Hershner 2015). Moreover, consistently being late in going to bed, frequent arousals, or early awakening may also contribute to sleep deprivation. Medical problems such as depression, obstructive sleep apnea, hormone imbalances, and other chronic illnesses may also be the reasons for sleep deprivation. There is no substitute for

restorative sleep, but some measures may prevent the implications of sleep loss. Therefore, a certain amount of attention is necessarily required to understand the clinical consequences and prevention from chronic sleep debt.

6.2 Sleep and Sleep-Loss-Associated Disorders

Sleep disorders, or "somnipathy," are diagnosed primarily based on three primary symptoms associated with altered sleep patterns. These symptoms are "insomnia, excessive sleepiness, and abnormal events that occur during sleep." Some sleep disorders trigger severe medical conditions and interfere with routine physical, mental, social, and emotional functioning. Therefore, we need to have a better understanding of different sleep disorders and their critical diagnostic criteria. On the other hand, sleep alteration is common in several disorders, even though it is hardly assessed during medical examinations. It is one of the crucial factors and must be asked routinely during the medical checkup. Otherwise, sleep problems may remain underdiagnosed, and patients may not get optimal treatment (Grandner and Malhotra 2015). For example, the sleep record may help a psychiatrist to diagnose mood and anxiety disorders, a cardiologist to detect it as a risk factor for cardiovascular diseases, an endocrinologist to characterize potential circadian disruptions, a rheumatologist in advising to improve quality of life and treatment, an obstetrician to evaluate the risk for complications, and a urologist to assess the impact of nocturia. It is, therefore, essential to have a better understanding of sleep and sleep-loss-associated disorders and their clinical implications.

6.2.1 Sleep Disorders

Sleep disorders are quite prevalent in children and adults because of the modern lifestyle. Astonishingly, about half of the elderly populations worldwide complain about sleep problems at some point. Therefore, an in-depth study of sleep disorders may provide a better understanding of their diagnosis and therapeutics. It may also help in establishing good communication between clinicians and researchers. Several factors, such as prediagnosed physiological problems, stress, a shift in circadian rhythms, aging, and medicine, significantly contribute to sleep disorders. The most common sleep disorders are insomnia, hypersomnia, parasomnia, narcolepsy, restless leg syndrome, periodic limb movement disorder, sleep apnea, circadian-rhythm-associated sleep disorders, sleep sex or sexsomnia, and so on. We have highlighted some of the sleep disorders here with their detailed diagnostic features.

6.2.1.1 Insomnia

Experiencing difficulties in falling asleep is widely categorized as "insomnia". It includes either having difficulty in initiating or maintaining sleep. It also includes extended periods of nocturnal wakefulness and frequent nocturnal awakening. A broad distinctive diagnosis includes repeated sleep-initiation difficulties, decreased

sleep duration, reduced sleep consolidation, or sleep quality even though the patients get adequate time and opportunity to sleep. Insomniac patients may tend to wake up early and may show no signs of restorative sleep (Edinger et al. 2004).

Several factors/conditions are associated with insomnia; therefore, it should be categorized based on causal factors. Insomnia is classified into two categories: (a) primary insomnia and (b) secondary insomnia (Edinger et al. 2004; Thorpy 2012). Insomnia is considered as primary insomnia when some intrinsic/extrinsic factors or both are associated with its etiology, and it is not the manifestation of any secondary factors or disorders. Acute insomnia (adjustment insomnia), behavioral insomnia, and inadequate sleep hygiene insomnia are some of the examples of primary insomnia. However, secondary insomnia occurs as a consequence of a medical or psychiatric illness, another sleep disorder, or substance abuse. The secondary insomnia is categorized as mental-disorder-associated insomnia, psychophysiological insomnia, paradoxical insomnia, idiopathic insomnia, sleep-apnea-associated insomnia, periodic-limb-movement-disorder-associated insomnia, and insomnia due to a medical condition and a drug or substance of abuse (Edinger et al. 2004; Thorpy 2012).

6.2.1.2 Hypersomnia

The symptoms of hypersomnia disorders are primarily excessive daytime sleepiness (EDS); however, nocturnal sleep remains normal. During the daytime, subjects show an inability to stay alert and awake during the usual wake periods. In the *Diagnostic and Statistical Manual of Mental Disorders (Vth edition)*, hypersomnia has been considered for symptoms of the prolonged nocturnal sleep episode and daily sleep amounts more than 9 h (Reynolds et al. 2010). It has also been suggested in the same manual that some other disorders may be present along with hypersomnia. Still, it may be necessary to treat hypersomnia before treating the main disease.

Recurrent or periodic hypersomnia is mainly referred to as two different categories: (a) Kleine–Levin syndrome and (b) menstrual-related hypersomnia. Kleine–Levin syndrome is a rare sleep disorder observed primarily in the adolescent. The main associated symptoms are intermittent hypersomnolence, hyperphagia, cognitive deficits, and, in some cases, hyperactivity and hypersexuality (Ramdurg 2010). Somnolence, hyperphagia, and withdrawal symptoms of Kleine–Levin syndrome sometimes mimic those of severe depression followed by a brief period of high manic energy; hence, it can be misdiagnosed for bipolar disorder. The episodes of hypersomnolence vary from a week to a couple of months. However, surprisingly, the conditions of subjects remain entirely asymptomatic between the episodes. Such conditions last for a few years; however, to date, no definite cause is known (Ramdurg 2010). Lhermitte first described menstruation-related periodic hypersomnia in 1942, and episodes of hypersomnolence overlapping temporally with menstrual cycles are the striking symptom of this disease (Bamford 1993; Raju 1997). Menstrual hypersomnia is a rare sleep disorder. It produces marked somnolence beginning a few days before the onset of and terminating in a few days of menstruation. It is also associated with emotional and behavioral changes. Although the cause of the disease is not known at all, it is assumed that altered sex hormones

during the menstrual period may dysregulate the central sleep–wake centers, which may induce episodes of excessive sleep (Raju 1997).

Another type of hypersomnia is called idiopathic hypersomnia. The patients with idiopathic hypersomnia show a remarkable increase in sleepiness, often accompanied by a prolonged nocturnal sleep but no alteration in REM sleep (Anderson et al. 2007). The patients exhibit symptoms of confusion, difficulty in waking up, and recurrence of sleep urge. It was defined as a distinct disease entity in 1979 in the *International Classification of Sleep Disorders* (ICSD) (Anderson et al. 2007). Idiopathic hypersomnia can be divided into two categories: (a) idiopathic hypersomnolence without long sleep time [EDS $>$ 3 months; nocturnal sleep $>$6 h but $<$10 h; mean sleep latency $<$8 min; and $<$ 2 sleep-onset REM sleep periods (SOREMP)] and (b) idiopathic hypersomnolence with long sleep time [EDS for $>$3 months; prolonged sleep time $>$10 h with difficulties in early morning wakening or from naps; sleep latency $<$8 min; and $<$2 SOREMP]. Idiopathic hypersomnia was described initially as chronic and interminable. However, there are some case reports where symptoms in some patients improved spontaneously (Anderson et al. 2007).

Hypersomnia can also be induced behaviorally. It is commonly called "behaviorally induced insufficient sleep syndrome" (BIISS) or "insufficient sleep syndrome." It is a form of hypersomnia that involves a voluntary restriction of nighttime sleep (behaviorally chosen nocturnal sleep restriction) as the person wants to perform activities such as job, study, and watching TV. BIISS is a leading cause of excessive daytime sleepiness and health problems such as fatigue, mood disorder, excessive eating, and weight gain (Williams et al. 2019).

6.2.1.3 Parasomnia

Sleep state accompanied by some physical or emotional sporadic events, such as abnormal sleep-related movements, emotional and behavioral incitement, and intense dreaming, are considered as parasomnias. These undesirable events do not occur frequently; instead, they appear sometimes during sleep. It is a belief that the parasomnias coincide with other sleep disorders, such as obstructive sleep apnea syndrome. The International Classification of Sleep Disorders (ICSD) classification has divided parasomnias into six groups of disorders (Table 6.1). These disorders may emerge from either NREM or REM sleep. Some of the parasomnias may appear due to drug or substance abuse or medical conditions (American Sleep Disorders Association 1997; Fleetham and Fleming 2014; Thorpy 2012).

Three frequent events that are typically associated with arousal from non-REM sleep are (a) confusional arousals, (b) disorientation, and (c) sleep terror. Confusional arousals/confusional behavior usually occurs during or after arousal from sleep. It is common in children and can also occur during daytime sleep. Disorientation is a complex behavior and can arise from sudden arousals from NREM sleep. Subjects sometimes start walking subconsciously. Sleep terror accompanies a cry or manifestation of extreme fear and scream. It also occurs from NREM sleep and is associated with hyperactivation of the autonomic system (Fleetham and Fleming 2014; Thorpy 2012).

Table 6.1 International classification of sleep disorders for parasomnia

1. Disorders of arousal from NREM sleep
(a) Confusional arousals
(b) Sleep walking
(c) Sleep terrors
2. Parasomnias usually associated with REM sleep
(a) Rapid eye movement sleep behavior disorder
(b) Recurrent isolated sleep paralysis
(c) Nightmare disorder
3. Other parasomnias
(a) Sleep-related dissociative disorders
(b) Sleep enuresis
(c) Sleep-related groaning
(d) Exploding head syndrome
(e) Sleep-related hallucinations
(f) Sleep-related eating disorder
4. Parasomnia, unspecified
5. Parasomnia due to drug or substance use
6. Parasomnia due to medical conditions

Some parasomnias are manifested at onset or during REM sleep. A few behavioral parasomnias are violent and associated with dream enactment. They are widely categorized as REM sleep behavior disorder (RBD). REM-sleep-associated muscle atonia is lost in REM sleep behavior disorder (can also be called "REM sleep without muscle atonia"). The negative dream enactment associated with violent fighting potentially causes injury to the sleeper or bed partner. Such episodes may initially occur about once a week but may go up to four times a night (Fleetham and Fleming 2014). Recurrent isolated sleep paralysis usually occurs at sleep or wake onset. Muscle activity is lost, and subjects cannot move; ventilation, however, remains unaffected. Subjects report hypnogogic or hypnopompic hallucination during sleep paralysis (Goode 1962; Sharpless and Barber 2011). In REM sleep nightmare disorder, nightmares frequently occur in REM sleep, and it awakens the subjects with intense anxiety and fear (Levin and Fireman 2002).

During the transition from wakefulness to sleep/N1–N2 stages of sleep to wakefulness, some of the integrative features, such as consciousness, identity, or perception of the environment and occasionally memory as well, are disrupted. Patients infrequently also get involved in physical or sexual abuse. Such parasomnias are considered as sleep-related dissociative disorders (Ağargün et al. 2001). Sleep enuresis (a repeated inability to control urination) occurs in some patients during sleep (Yeung 2003). Sleep-related groaning [catathrenia: end-inspiratory apnea (breath holding) and expiratory groaning; the sound is produced during exhalation as opposed to snoring, which occurs during inhalation)] is a rare, unusual disorder. The patients remain unaware of the events, and also the pathophysiology is unknown (Vetrugno et al. 2008). Some patients have reported that they had an experience of

loud or explosive noise in their heads as they were falling asleep or at wake onset. Such disorder has been characterized as "exploding head syndrome" (Chakravarty 2008).

In sleep-related eating disorder (SRED), patients exhibit recurring episodes of eating during the transition from sleep to arousal. The urge to eat remains so high that the patients take high-caloric foods in an out-of-control manner. The patients hardly remain aware of the events that they were eating periodically while asleep. SRED is also occasionally associated with psychotropic medication and some other sleep disorders, such as narcolepsy and restless legs syndrome (Vinai et al. 2012).

6.2.1.4 Narcolepsy

Narcolepsy is also associated with excessive daytime sleepiness, and hypersomnia is the most common symptom of narcolepsy. Sleep attacks occur despite having sufficient nocturnal sleep. Daytime sleep occurs daily, recurring typically every 2 h (can vary). The sleep episodes have several characteristics; for example, it is often irresistible, despite the individual making desperate efforts to fight the urge to sleep, and sleep duration is usually short (although it can vary with environmental factors) and frequently is associated with dreaming. The refreshing value of short naps is of considerable diagnostic importance, except in children who are often tired of waking, and severe sleepiness can also lead to unconscious microsleep episodes (Baumann et al. 2014).

Narcolepsy can be with or without cataplexy (Baumann et al. 2014; Billiard 2007). Cataplexy is defined as sudden and transient episodes (<2 min) of loss of muscle tone. It is generally bilateral and triggered by emotions (usually laughing and joking). The main diagnostic criteria for narcolepsy with cataplexy are excessive daytime sleepiness occurring almost daily for at least 3 months. The patients can occasionally have "status cataplecticus," which comprises recurrent cataplectic episodes lasting several hours. Mean daytime sleep latency is 8 min or shorter, with two or more sleep onset in REM periods (SOREMP) (the time from sleep onset to REM sleep should be less than 15 min in atleast two naps). Alternatively, hypocretin-1 concentration in the CSF should be 110 ng/L or lower. It is believed that the loss of hypocretin neurons in the lateral hypothalamus is the main cause of narcolepsy. However, in some patients with narcolepsy with cataplexy (<10%), the hypocretin levels are found to be normal. Hypocretin receptors may be altered, or some other pathophysiological mechanism could be associated (Billiard 2007). In 1999, a mutation in the gene coding for hypocretin type 2 receptors was identified as the cause of familial canine narcolepsy, but not in sporadic canine narcolepsy (Dauvilliers and Tafti 2006; Ripley et al. 2001). Furthermore, a decreased concentration of hypocretin-1 in the CSF and brain in sporadic narcolepsy has also been reported (Dauvilliers et al. 2007; Dauvilliers and Tafti 2006).

6.2.1.5 Sleep Apnea

Sleep apnea is a sleep-related breathing disorder, and a person's breathing is interrupted during sleep. It is categorized into two types: (a) obstructive sleep apnea and (b) central apnea (Strollo and Rogers 1996). In obstructive sleep apnea,

the upper airway pathway is obstructed, which causes increased effort in breathing and inadequate ventilation. The adult suffering from obstructive sleep apnea, recurrent cessation in breathing episodes (apneas), or upper airway obstruction (hypopneas) has been observed at sleep onset or during sleep. As a result of an obstruction in breathing, the blood oxygen saturation is reduced, and subjects experience frequent arousal. The obstructive sleep apnea in children also has the same symptoms. However, they do not show frequent arousal, possibly because of a higher arousal threshold (American Academy of Sleep Medicine Task Force 1999; Strollo and Rogers 1996).

In central sleep apnea, respiration is altogether stopped intermittently or cyclically during sleep because of dysfunction in neural circuitries of the central nervous system (Eckert et al. 2007). It is further characterized into two forms: (a) primary central sleep apnea and (b) secondary central sleep apnea (Eckert et al. 2007). The cause of primary central sleep apnea is not known. It is mainly characterized by the symptom of recurrent cessation of breathing episodes during sleep, and subjects do not put effort into breathing. The diagnostic symptoms of primary central sleep apnea are excessive daytime sleepiness, insomnia, or difficulty in breathing during sleep (5 or more apneic episodes per hour of sleep); PCO_2 should be ~45 mm Hg (hypercapnia should not be observed) (American Academy of Sleep Medicine Task Force 1999; Eckert et al. 2007). If the central sleep apnea is caused by the long-term use of a drug or substance of abuse, then it is referred to as secondary central sleep apnea. It is generally caused because of long-term consumption of opioids, which suppresses respiration by acting on the medullary respiratory neurons. Often, premature infants suffer from sleep apnea, usually referred to as apnea of prematurity (sudden respiratory pause lasting for atleast 20 s or more along with bradycardia). However, a few infants suffer from similar sleep apnea, referred to as apnea of infancy, but the reasons remain unknown. Such problems could be a developmental pattern, or it may be secondary to other medical disorders (American Academy of Sleep Medicine Task Force 1999; Durand et al. 1985).

6.2.1.6 Restless Leg Syndrome and Periodic Limb Movement Disorder

Restless leg syndrome is one of the painful sensorimotor neurological sleep-associated disorders (Thorpy 2012). The subjects feel an extreme urge to move extremities, mostly the legs, during sleep as the subjects feel unpleasant sensations or pain in the affected limbs. The periodicities of leg movement increase by evening and worsen during sleep. As a result, subjects experience very disturbed sleep and ultimately seek medical relief from annoyance during sleep. Several studies have indicated that the incidence of disorders increases with aging. It has been reported that there are 9–20% prevalence of restless leg syndrome and 4–11% prevalence of periodic limb movement disorder in old adults (Hornyak and Trenkwalder 2004; Thorpy 2012).

Restless leg syndrome and periodic limb movement disorder are sleep disorders and may appear similar at first look, but they are entirely different (Hornyak and Trenkwalder 2004; Thorpy 2012). In periodic limb movement disorder, the patients move either one or both legs rhythmically several times in the night. Subjects,

however, may not know if they are having the condition of any rhythmic leg movement during sleep, whereas, in restless leg syndrome, the patients have an uncontrollable urge to move their one leg only (either left or right leg), and other parts are rarely involved. More so, the patients feel pain and an uneasy sensation or a feeling of something crawling on their legs before or at sleep onset. Also, periodic limb movement disorder is involuntary, and patients can sleep while having movement episodes. Nevertheless, the restless leg syndrome keeps the patients awake because of jerky and painful leg movement (Thorpy 2012).

6.2.1.7 Circadian-Rhythm-Associated Sleep Disorders

The circadian-rhythm-associated sleep disorders involve a persistent or recurrent alteration between circadian and sleep timing. Patients suffering from this disorder are unable to sleep at actual bedtime. The sleep–wake cycle is misaligned with circadian timing. Therefore, the patients complain of either insomnia or excessive sleepiness. In the phase delay sleep disorder, the sleep periods are always delayed in comparison to normal sleep timing, which is very common in adolescents (Saxvig et al. 2012; Weitzman et al. 1981). On the other hand, the old adults with advanced sleep phase disorder, the sleep period always occurs before actual bedtime (Moldofsky et al. 1986; Sack et al. 2007). The circadian rhythm associated with sleep disorders is possibly linked with a lack of daylight exposure, which acts as a synchronizing agent for circadian rhythm (Thorpy 2012).

Sleep disturbance because of the jet lag (jet lag disorder) is attributed to a temporal incompatibility between the sleep–wake cycle timing through the circadian clock and rapid change in time zones (Arendt 2009; Sack 2010). Similarly, working in night shifts also influences sleep–wake timing, and the subject may complain of insomnia or excessive daytime sleep (Akerstedt 2003; Wright et al. 2013).

6.2.1.8 Sexsomnia (Sleep Sex)

Sexsomnia is a unique type of parasomnia, which is diagnosed by atypical sexual behavior during sleep (Béjot et al. 2010; Ebrahim 2006). Very few reports are available, but the majority of them have considered it a type of sleep-walking disorder (Béjot et al. 2010; Ebrahim 2006). Most of the subjects with sexsomnia have a family history of parasomnia and sleep-walking (Béjot et al. 2010; Ebrahim 2006). Sexual behavior during sleep varies from sexual vocalizations (dirty talk) to sexual assault. The England Court acquitted an offender of three times rape charges after considering his petty condition of suffering from sexsomnia. Sexsomnia is a very uncommon parasomnia, and it is believed to be associated with NREM sleep (Dubessy et al. 2016; Ebrahim 2006).

6.2.2 Sleep-Loss-Associated Disorders

Altered sleep architecture has been reported in several disorders, such as mood and anxiety disorders, physiological disorders, metabolic disorders, chronic diseases, and frailty. It is believed that symptoms of sleep disturbance and its magnitude may

predict the incidences of relapse of some of the diseases. For example, unrelenting insomnia is the residual symptom in depressive patients, and it remains a higher risk of subsequent depression (Nutt et al. 2008). Also, sleep management in major depressive disorder (MDD) and generalized anxiety disorder (GAD) patients improves anxiety and mood (Pollack et al. 2008; Stein and Lopez 2011). Clinical interventions for sleep disturbances have also been recommended as therapeutics to reduce the risks of frailty in the elderly (Piovezan et al. 2013, 2015). Therefore, it is likely that sleep management in some of the patients could be a beneficial therapeutic. Here, we have highlighted some of the diseases where sleep management could be promising therapies.

6.2.2.1 Sleep Alteration and Anxiety Disorders

Several studies have demonstrated that sleep-disruption-specific treatments may improve anxiety and mood in depressive patients. Hypnotic drugs, in combination with antidepressant treatment, induce additional benefits in improving depressive symptoms compared with subjects given only antidepressant drugs (Rumble et al. 2015). Hence, medication/treatment for improving sleep quality is nowadays becoming a promising tool to help improve the outcomes (Fang et al. 2019). The pretreatment insomnia symptoms in some depressive patients are believed to be linked with poorer treatment outcomes of a single antidepressant drug (Sung et al. 2015). Furthermore, Dr. Michael Irwin's group has proposed that the risk for depression could be more in the elderly population if they have a prior history of the disorder. However, in those having a prior history of depression, posttreatment sleep disturbance could predict a relapse/recurrence of depressive disorder (Lee et al. 2013). Hence, optimization of the efficacy of sleep-related intervention may help improve depression and also prevent late-life depression in the elderly population (Lee et al. 2013). Sleep disturbance is a significant risk factor for increasing depression in HIV-infected nondepressed patients. It was observed that HIV+ patients with chronic sleep disturbances significantly increased depression within 6 months compared to HIV+ patients with no sleep disturbances. Targeting insomnia treatment may likely have decreased depression in HIV+ patients (Irwin et al. 2018). All these together suggest that sleep management may help improve anxiety and mood in depressive patients.

6.2.2.2 Sleep Alteration and Reactive Aggression

In clinical observations, it has been explored that sleep problems could be a causal factor for reactive aggression and violence. Several studies in animals and humans have demonstrated a significant relationship between poor sleep and reactive aggression (Hsu et al. 2009; Jha and Mallick 2009; Kamphuis et al. 2012; Madan and Jha 2012). Poor sleep does not provoke physical aggression in all subjects; however, psychiatric patients are quite sensitive to an emotional outbreak with sleep deprivation. Such violent behavior could be mediated by the negative effect of sleep alteration on the cortical neurons (Kamphuis et al. 2012). In addition, sleep problems and aggression and violence could also be linked with alteration in the central serotonergic and the hypothalamic–pituitary–adrenal axis in psychiatric patients

(Barden 2004; Jha et al. 2001). Hence, it has been proposed that it would be essential to identify the individuals at risk, and offering sleep management therapies may reduce aggressive and violent incidents (Kamphuis et al. 2012).

6.2.2.3 Sleep Alteration and Chronic Diseases

Poor sleep quality and chronic fatigue are common among patients suffering from chronic diseases such as rheumatoid arthritis and fibromyalgia. Rheumatoid arthritis and fibromyalgia are chronic medical conditions, and patients undergo an unremitting joint and widespread musculoskeletal pain (Roizenblatt et al. 2011; Szady et al. 2017). Patients report the feeling of exhaustion, weakness, and sleep disturbances even during the early stages of the diseases (Roizenblatt et al. 2011; Szady et al. 2017). Poor nocturnal sleep is an indicator of painful day, but at the same time, more painful conditions induce more sleep disturbances (Affleck et al. 1996). The patients suffering from chronic pain in rheumatoid arthritis and fibromyalgia also report sleep disturbance, mainly nonrestorative sleep and morning stiffness (Wolfe et al. 1990).

Interestingly, Szady et al. have observed a significant correlation between sleep quality and pharmacological treatments. They have reported that sleep quality in rheumatoid arthritis patients significantly improves with combinatorial drug treatment such as conventional drugs (NSAIDs, glucocorticosteroids, immunosuppressive drugs) along with biological drugs (TNF inhibitors, B-cell inhibitors, IL inhibitors, and T-cell inhibitors) compared to patients treated with only conventional drugs (Szady et al. 2017). Interestingly, it has been found that melatonin supplement given as a drug reduces fibromyalgia, headaches, irritable bowel syndrome, chronic back pain, and rheumatoid arthritis (Citera et al. 2000; Danilov and Kurganova 2016). Melatonin is primarily a circadian rhythm regulator and a potent sleep inducer. It performs several other functions such as antioxidant, oncostatic, immunomodulating, normothermic, and anxiolytic functions; in addition, it helps improve sleep quality as well as fibromyalgia and rheumatoid arthritic conditions in patients (Danilov and Kurganova 2016). The above set of studies suggests that it is very likely that improving sleep quality in patients suffering from some of the chronic diseases may help in recuperation.

6.2.2.4 Sleep Alteration and Frailty in the Elderly

Elderly people face disruptions in the circadian rhythm as well as in the sleep cycle. Old adults experience reduced exposure of daytime light as well as sleep amount (Scheuermaier et al. 2010). The exposure of reduced daylight alters the nocturnal pineal melatonin levels, which influences both the circadian function and the sleep–wake cycle (Van Someren 2000). In the elderly, a high prevalence of frailty syndrome is primarily attributed to low sleep quality and sleep efficiency, excessive daytime sleepiness, and sleep disorder breathing (Ensrud et al. 2012, 2009a; Vaz Fragoso et al. 2009). It has also been reported that the frailty status in the elderly significantly correlates with longer sleep latency and daytime sleepiness (Alessi and Schnelle 2000). It is possible that instability in the circadian system affects the sleep–wake cycle, which may, in turn, persuade frailty in the elderly.

Moreover, several biological metabolic pathways are altered with the advancing age. The first apparent changes that appear with aging are hormonal imbalance, compromised immune system, oxidative stress, and mood disorders. With aging, growth hormone and testosterone secretions diminish, the pro-inflammatory system is activated, and the rate of oxidative stress increases. Also, chronic sleep loss and aging both independently influence the functions of hypothalamic–pituitary–adrenal and hypothalamic–pituitary–gonadal axes (Bonavera et al. 1998; Gaffey et al. 2016; Gruenewald et al. 2000; Lee et al. 2019; Minkel et al. 2014). An altered sleep–wake cycle reduces the levels of cortisol, testosterone, and estrone but increases the levels of progesterone, prolactin, corticosterone, and ACTH (Andersen et al. 2005). Hence, it has been argued that the increased risk of morbidity and mortality of frailty is intricately linked with sleep disturbances in old adults (Barrett-Connor et al. 2008; Ferrie et al. 2013; Patel et al. 2009).

Increased incidences of hospitalization, falls, disability, and higher mortality rates in the elderly are primarily attributed to frailty (Cawthon et al. 2007; Ensrud et al. 2009b). Frailty weakens major bodily systems, if not all, such as the musculoskeletal, cardiovascular, and nervous systems. That is why it has been acclaimed as a significant factor that causes disability in elderly subjects (Daniels et al. 2008). Furthermore, the sedentary lifestyle significantly contributes to both frailty and sleep alteration (de Castro Toledo Guimaraes et al. 2008; Nobrega et al. 2014). Therefore, finding ways for frailty prevention is of clinical interest. Puts et al. have observed that interventions such as physical activity, physical activity combined with nutrition, physical activity along with nutrition and memory training, home modifications, prehabilitation (physical therapy including exercise and home modifications), and comprehensive geriatric assessment (CGA) significantly reduce frailty and its consequences in elderly (Puts et al. 2017). The clinical interventions for sleep disturbances such as continuous positive airway pressure therapy for OSA, bright light therapy, and other strategies for insomnia have also been recommended as therapeutics to reduce the risks of frailty in elderly (Piovezan et al. 2013, 2015).

6.3 Clinical Implications

As discussed above, sleep disturbance is prevalent in the majority of clinical conditions. The severity and clinical implications of insomnia are anticipated based on their correlates, such as time to fall asleep, duration of awakenings, total sleep time, frequency, and duration of sleep difficulties. Subjects also complain of daytime sleepiness, tiredness, cognitive impairments, mood disturbances, and so on. Such complexities prompt subjects to seek clinical interventions.

There are primarily two main avenues of treatment for sleep deprivation: (a) behavioral and cognitive measures and (b) pharmacological interventions. There are several effective methods to enhance sleep that does not require medication. These are as follows:

Relaxation techniques: Progressive muscle relaxation involving tensing and untensing different muscles in the body to help calm the body. Meditation techniques, mindfulness training, breathing exercises, and guided imagery can also help in this area. Audio recordings are available that can help a person fall asleep at night.

Stimulation control: This involves controlling pre-bedtime activities and surroundings to moderate the sleeping pattern. For example, persons controlling their stimulus would spend time in bed only when they feel sleepy, which controls the association between being in bed and feeling ready to sleep.

Cognitive-behavioral therapy (CBT): This is a type of treatment designed to help people understand and change the thought patterns behind certain behaviors. It can challenge beliefs that may not be healthy and promote rational, positive thought. CBT can help a person to develop a healthier sleeping pattern.

The sleep disorder clinics were established in the early 1970s. Since then, the measurement of daytime sleepiness and alertness has become a primary tool for diagnosing and describing sleep disorders, particularly disorders of excessive somnolescence. The assessment of alertness has also been used to investigate problems in many areas of basic and clinical research. Presently, the techniques most commonly used to evaluate sleep abnormalities, both experimentally and clinically, are the following:

1. **Overnight polysomnography (OPSG):** OPSG is an overnight recording of the patient's sleep patterns. Physiological variables, that is, EEG, EOG, EMG, respiratory airflow, respiratory excursion, and lower limb movement, are recorded continuously and simultaneously during sleep. Following are the abnormalities related to REM sleep: elevated submental electromyographic (EMG) tone or excessive phasic submental or limb EMG twitching; documentation of abnormal REM sleep behaviors during OPSG studies (e.g., prominent limb or truncal jerking); and complex, vigorous, or violent acts or histories of injurious or disruptive sleep behaviors.
2. **Multiple sleep latency test (MSLT):** MSLT is for patients complaining of excessive sleep disturbance, daytime fatigue, or excessive daytime sleepiness, as is found in narcoleptic patients. Repeated measurement of sleep latency across a day provides direct access to the diurnal fraction of the sleep–wake interaction, which is of fundamental concern to the sleep specialist. Standard sleep studies usually include both tests, OPSG (may be performed over several nights) followed by MSLT the next day.

6.4 Conclusion

In summary, sleep disturbance is a global public health problem, which is associated with several clinical conditions. If an individual fails to attain the minimum daily recommended time in sleep, he or she may be sleep deprived, which could be

intentional or unintentional. As mentioned above, teenagers and young adults most likely become intentionally sleep deprived. A few subjects may not obtain proper sleep unintentionally because of their profession and obligations. There are several other reasons for sleep deprivation, such as depression, obstructive sleep apnea, hormone imbalances, and other chronic illnesses. There is no substitute for restorative sleep, but some measures may prevent the consequences of sleep loss. Therefore, a certain amount of attention is mainly required to understand the clinical implications and prevention from chronic sleep debt. Prevalence and morbidity data explain that it is an uncompromising medical condition. The resolution requires attention from all walks of life, including health technology, caregivers, and from the community.

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