Sushil K. Jha · Vibha M. Jha *Editors*

Sleep, Memory and Synaptic Plasticity

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Editors
Sushil K. Jha
Sleep Research Laboratory, School of Life Sciences
Jawaharlal Nehru University
New Delhi, India

Vibha M. Jha
Sleep Research Laboratory, School of Life Sciences
Jawaharlal Nehru University
New Delhi, India

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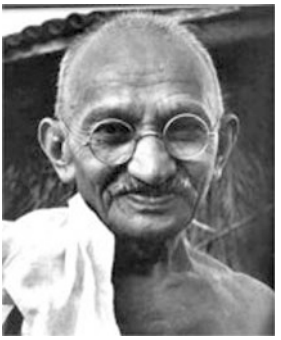

Each night, when I go to sleep, I die. And the next morning, when I wake up, I am reborn.

Mahatma Gandhi

A spiritual chant in Indian mythology for a good night's sleep:

या देवी सर्वभूतेषु निद्रारूपेण संस्थिता ।
नमस्तस्यै नमस्तस्यै नमस्तस्यै नमोनमः ।।

Ya Devi Sarva bhuteshu Nidra Roopen Sanstithah

Namastasyai Namastasyai Namastasyai Namo Namah

(O Goddess, you are omnipresent. You also exist in sleep. I bow to you.)

Preface

Most animals spend a significant amount of time in sleep, yet its core functions are mostly unknown. There is increasing evidence suggesting that sleep helps in memory consolidation and induction of neural plasticity. In several studies, it has been demonstrated that short-term deprivation of either total sleep or rapid eye movement (REM) sleep alone soon after a learning task induces memory deficit. Quantitative and qualitative changes in sleep architecture after different training tasks further suggest that discrete memory types may require a specific sleep stage(s) for optimal memory consolidation. For example, in rodents, non-REM (NREM) sleep, slow-wave activity, and sleep spindle density during NREM sleep increased after fear conditioning, odor–reward association, and motor learning tasks, respectively. In humans, similar results have been reported after verbal memory retention and motor-skill learning tasks. Nevertheless, REM sleep increases explicitly more after learning some specific tasks, such as spatial learning tasks, negative and positive reinforcement tasks, avoidance tasks, etc. These studies suggest that a particular sleep stage or total sleep facilitates and optimizes memory formation after training.

Sleep plays an essential role in the induction of synaptic plasticity. Synaptic plasticity is defined as changes in the strength, number, and size of the synapses and/or changes in morphological structures in the synapse, i.e., changes in the number of dendritic spines. Studies suggest that the amygdala neurons manifest necessary plastic changes after conditioning to fearful cue. Interestingly, such physiological plasticity acquired during wakefulness is further re-expressed during sleep, suggesting that the sleeping brain reinforces neural encoding. Additionally, it has been shown that sleep deprivation alters synaptic plasticity and membrane excitability in the hippocampal neurons and synaptic up-scaling in the cortical neurons. It promotes ocular dominance plasticity in the visual cortex in developing cats. These findings suggest that sleep plays an essential role in the induction of synaptic plasticity, which is one of the underlying mechanisms of memory consolidation.

Several epidemiologic studies have demonstrated a close link between chronic sleep loss and changes in basal metabolic rate, which ultimately contributes to inducing obesity and diabetes. On the other hand, the prevalence of hypertension

is higher in patients with sleep breathing disorder such as obstructive sleep apnea. Some studies suggest that the immune system gets compromised after sleep deprivation making a subject susceptible to infections. Abnormal bacterial overgrowth in the intestine, polymicrobial infection of the mesenteric lymph nodes, and increased invasion of extraintestinal body tissues observed during sleep deprivation suggest that sleep deprivation does affect the immune system. All these studies indicate the functional benefits and the essential role of sleep in maintaining good health, processing of memory information, and several other functions.

In this book, we have covered the functions of sleep in a broader perspective. The book focuses on the memory function of sleep and examines sleep-dependent consolidation across declarative, procedural, and emotional memory domains. The transformation of sleep from the prenatal stage to adulthood and how the functions of sleep may change across an individual's life-span have also been discussed. The book provides the conceptual framework on the potential countermeasures for the amelioration of sleep-deprivation-induced malfunctions from behavioral to molecular levels. Both acute and chronic sleep loss as well as sleep fragmentation affect neurons at the molecular level leading to injury and sometimes death. We have discussed the potential role of sleep in the maintenance of ionic homeostasis and acid-base balances. We have addressed how chronic and acute sleep loss can cause ionic imbalances and cellular distress, which, in turn, may affect cognitive ability. The book summarizes critical evidence that supports the role of sleep in brain plasticity and provides insight into the underlying mechanisms. It includes indirect evidence, which comes from studies of how sleep influences perception, learning, and memory, and direct evidence, which are physical measures of synapse number or strength before and after sleep. The potential roles of different types of learning, stress resilience, vulnerability, and neurobiological substrates that regulate the interaction of stress and sleep and the formation of traumatic memories are discussed in detail.

New Delhi, India

Sushil K. Jha
Vibha M. Jha

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About the Editor

Sushil K. Jha is currently working as an Associate Professor at the School of Life Sciences at the prestigious Jawaharlal Nehru University (JNU), New Delhi, India. He obtained his Ph.D. from Hamdard University in 2001 and subsequently worked as a Postdoctoral Fellow and Research Associate at the University of Pennsylvania, Philadelphia, USA, from 2001 to 2007. In 2007 he was appointed Assistant Professor at JNU and was promoted to the rank of Associate Professor in 2013.

He is one of the few scientists in India currently working on the neuronal and physiological aspects of sleep and its impact on overall mental and physical health at the molecular level. He has been able to show, at the molecular level, the importance of sleep for memory functions and its implications for the immune system. Dr. Jha has published 26 research papers in respected international journals and contributed chapters in 6 different books published by leading publishers, including Oxford and Cambridge University Press.

Among the various prestigious awards that he has received, one of the notable is the NASI Scopus Young Scientist Award in 2007 from Elsevier. He is also the recipient of the American Sleep Medicine Foundation's Faculty Career Development Award in 2005.

In order to raise awareness among people regarding the importance of sleep for proper brain function and memory, he has periodically appeared on national television and also published articles in national newspapers.

Dr. Vibha M. Jha earned her Ph.D. from Jawaharlal Nehru University in 2005 and subsequently worked as a Postdoctoral Fellow at the University of Pennsylvania, Philadelphia, USA. She has worked in Dr. Adrian Morrison's lab in the Department of Animal Biology, School of Veterinary Medicine UPENN, Philadelphia, USA. Dr. Jha has published several research papers in reputed international journals and contributed chapters in different books. She is a recipient of several awards and gold medals, such as Dr. Ramji Narain Omvati Gold Medal and Panjab University Medal for standing first in M.Sc. (H.S.). She is engaged in sleep research since 1999 and has contributed significantly to the field of sleep research.

Contributors

Anjali Sleep Research Laboratory, School of Life Sciences, Jawaharlal Nehru University, New Delhi, India

Luigi De Gennaro Department of Psychology, Sapienza University of Rome, Rome, Italy

Michele Ferrara Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy

Marcos G. Frank Elson S. Floyd College of Medicine, Washington State University Spokane, Spokane, WA, USA

Sushil K. Jha Sleep Research Laboratory, School of Life Sciences, Jawaharlal Nehru University, New Delhi, India

Vibha M. Jha Sleep Research Laboratory, School of Life Sciences, Jawaharlal Nehru University, New Delhi, India

Deepika Kant Sleep Research Laboratory, School of Life Sciences, Jawaharlal Nehru University, New Delhi, India

Krishna Kishore Neurophysiology Division, Defence Institute of Physiology & Allied Sciences (DIPAS), Defence Research and Development Organization (DRDO), Delhi, India

Laura Burton Faina Kurdziel Department of Psychology, Merrimack College, North Andover, MA, USA

G. Lonart Department of Pathology and Anatomy, Eastern Virginia Medical School, Norfolk, VA, USA

Fayaz Ahmad Mir School of Life Science, Jawaharlal Nehru University, New Delhi, India

Nirinjini Naidoo Center for Sleep and Circadian Neurobiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

Usha Panjwani Neurophysiology Division, Defence Institute of Physiology & Allied Sciences (DIPAS), Defence Research and Development Organization (DRDO), Delhi, India

Munazah F. Qureshi Sleep Research Laboratory, School of Life Sciences, Jawaharlal Nehru University, New Delhi, India

Koushik Ray Neurophysiology Division, Defence Institute of Physiology & Allied Sciences (DIPAS), Defence Research and Development Organization (DRDO), Delhi, India

R. J. Ross Research and Development Service, Corporal Michael J. Crescenz Veterans Affairs Medical Center, Philadelphia, PA, USA

Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

L. D. Sanford Sleep Research Laboratory, Eastern Virginia Medical School, Norfolk, VA, USA

Department of Pathology and Anatomy, Eastern Virginia Medical School, Norfolk, VA, USA

Shweta Tripathi Sleep Research Laboratory, School of Life Sciences, Jawaharlal Nehru University, New Delhi, India

Shweta Tripathi Sleep Research Laboratory, School of Life Sciences, Jawaharlal Nehru University, New Delhi, India

Valentina Socci Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy

Daniela Tempesta Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy

Meetu Wadhwa Neurophysiology Division, Defence Institute of Physiology & Allied Sciences (DIPAS), Defence Research and Development Organization (DRDO), Delhi, India

L. L. Wellman Sleep Research Laboratory, Eastern Virginia Medical School, Norfolk, VA, USA

Department of Pathology and Anatomy, Eastern Virginia Medical School, Norfolk, VA, USA

Chapter 1
The Memory Function of Sleep Across the Life Span

Laura Burton Faina Kurdziel

Abstract Sleep is the single most common form of human behavior, indicating that sleep likely has an important evolutionary function. Yet the functions of sleep are still debated. Intriguingly, sleep is not static across the life span, changing in duration, pattern, structure, and physiology. This chapter reviews the transformations of sleep, from the first appearance of sleep prenatally to sleep in older adulthood, and assesses how the functions of sleep may change in response. This review focuses on the memory function of sleep and examines sleep-dependent consolidation across declarative, procedural, and emotional memory domains. With respect to the memory function of sleep, changes in SWS in particular appear to have the greatest impact on the resultant age-related alterations in sleep-dependent memory consolidation.

Keywords Sleep · Development · Adolescence · Aging · Slow Wave Sleep · Memory

1.1 Introduction

Across the human life span, approximately a quarter of a century is spent asleep (Martin 2002). This makes sleep the most prevalent of all human behaviors. Why so much of life is dedicated to this behavior, during which no resources or reproductive mates can be attained, is one of the greatest unsolved scientific mysteries. Researchers have debated the function, or functions, of sleep for years (Franken et al. 2009). Studies have examined the role of sleep through many different lenses, including but not limited to genetic, neurological, immunological, behavioral, and epidemiological perspectives. The aim of this chapter is not to attempt to answer the question of why we sleep, nor to be a comprehensive review of all of the potential functions of sleep. Rather, this chapter will examine how these potential functions of

L. B. F. Kurdziel (✉)
Department of Psychology, Merrimack College, North Andover, MA, USA
e-mail: kurdziell@merrimack.edu

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sleep may change throughout the life span, as individuals progress from early prenatal development to older adulthood. This chapter will also center primarily on these changes throughout human development and with an additional focus on the way sleep may impact cognition and memory.

1.2 Young Adults

1.2.1 Sleep in Young Adults

Sleep is defined as a reversible period of behavioral quiescence with a high arousal threshold (Carskadon and Dement 2005). The adult form of sleep will be considered a baseline from which to compare the development and degradation of sleep across the life span. As such, it is important to describe the architecture and neural underpinnings of adult human sleep.

Sleep is not a static behavioral state. Adult human sleep can be subdivided into two states, rapid eye movement (REM) sleep and non-REM (nREM) sleep. Further, nREM sleep can be subdivided into three sleep stages: nREM1, nREM2, and nREM3 (nREM3 is also known as slow-wave sleep (SWS)). Each sleep stage is physiologically unique and can be characterized through polysomnography (PSG), a montage of electroencephalogram (EEG) waveforms, muscle movements measured by electromyogram (EMG), and eye movements as measured by electrooculogram (EOG; Carskadon and Dement 2005).

In healthy adults, sleep is entered through nREM and characteristically progresses in order of sleep depth (nREM1, followed by nREM2, and then SWS). REM sleep does not usually occur for at least 80 min, after which nREM and REM sleep alternate in cycles lasting approximately 90 min each (Carskadon and Dement 2005). Typically, total sleep time is about 7–8 h in a healthy young adult. While there may be trait-like inter-individual differences (Tucker et al. 2007), as well as potential sex differences (Mongrain et al. 2005) in sleep physiology, the architecture of sleep staging appears to be fairly consistent. Sleep architecture has also been shown to be stable across both morning and evening chronotypes (Mongrain et al. 2005).

The transition from waking to nREM sleep is generated in the hypothalamus (Siegel 2009). During this transition, there is a global reduction in neuronal firing rates, as well as more specific regional reductions (e.g., frontal gyri, anterior cingulate cortex, posterior putamen, caudate nucleus, midbrain, basal forebrain, and inferior cerebellar hemispheres; Braun et al. 1997; Kaufmann et al. 2006). The global reduction of neuronal activation is a result of GABA input from the thalamic reticular nucleus (Steriade 2001). Specifically, the sensory-relay function of the thalamus is inhibited, thus contributing to the unconscious state and to the high arousal threshold that defines sleep. Contrarily, endogenous cortico-cortical neuronal activation increases in nREM sleep (Steriade 2000, 2001).

Slow oscillations, oscillatory waves in the 0–1 Hz frequency range, are a core feature of nREM sleep. They are the result of cortical neurons cycling through an

extended hyperpolarization (downstate) phase, followed by a phase of spontaneous and intense neuronal firing (Steriade 2000, 2001). This intense state of depolarization (upstate) also plays a major role in synchronizing neuronal activity across the cortex as well as additional subcortical structures.

For example, the upstate of the slow oscillation synchronizes the initiation of thalamic sleep spindles. Sleep spindles are bursts of activity in the sigma (10–16 Hz) frequency range that can be observed in nREM sleep. Spindles originate from inhibitory thalamic reticular neurons, of which activation leads to bursting in linked cortical neurons (Achermann and Borbély 1997; De Gennaro and Ferrara 2003; Schabus et al. 2007). The resultant depolarization of cortical neurons from sleep spindles has been suggested to lead to intensive calcium influx, which in turn activates a number of processes within the neuron necessary for long-term potentiation (Ghosh and Greenberg 1995), such as calcium/calmodulin-dependent protein kinase II (CaMKII; Soderling and Derkach 2000; Lisman et al. 2002). Thus, sleep spindles have been specifically implicated in synaptic plasticity of excitatory neurons (Steriade and Timofeev 2003) and in learning and memory more generally (Fogel et al. 2007a; Fogel and Smith 2011; Ulrich 2016).

The upstate of the slow oscillation is also critical for synchronizing hippocampally generated sharp wave ripples. Sharp waves are synchronous bursts of incredibly high-frequency (~200 Hz) activation that progress from pyramidal neurons in the CA3 to the CA1 regions of the hippocampus during SWS (Buzsáki 1989). These events are thought to represent a wide-scale hippocampal network search for previously experienced patterns of activation. Due to this neurological rehearsal of previous experiences, the sharp waves are considered critical to learning and memory trace formation (Buzsáki 1989; Girardeau and Zugaro 2011). Importantly, sharp wave ripples are temporally coupled with slow oscillations that can recruit large networks of neurons and thus organize activation across multiple neurological structures. In addition, the slow oscillation synchronizes the hippocampal ripples with thalamocortical sleep spindles, further supporting the communication between the cortex and the hippocampus during SWS (Siapas and Wilson 1998; Clemens et al. 2007; Mölle et al. 2009).

The interplay between hippocampal, thalamic, and cortical networks through slow oscillatory synchronization of ripples and sleep spindles is associated with cortical synaptic plasticity. This relationship is also thought to be a possible mechanism through which hippocampal-dependent short-term memories are transferred to the more stable cortical storage of long-term memories (Gais et al. 2002; Schabus et al. 2004, 2007; Sirota and Buzsáki 2005; Wierzynski et al. 2009; Mölle et al. 2009; Born and Wilhelm 2012). In further support of this association, experimentally boosting the slow oscillation has been shown to enhance the consolidation of newly formed memories (Marshall et al. 2006).

Another commonly used analytic feature of nREM sleep is slow-wave activity (SWA). SWA is a measure of power in the delta frequency range (0.5–4 Hz) and is often considered a gauge of homeostatic sleep pressure (Achermann et al. 1993; Borbély 2001). The intensity of SWA builds over the course of the day. During the first nREM bout of the night, SWA is greatest in the frontal regions of the brain, an

effect that is especially observable following sleep deprivation (Werth et al. 1997; Finelli et al. 2001). Across subsequent bouts of nREM sleep, SWA is progressively reduced (Achermann and Borbély 1990; Achermann et al. 1993). Greater SWA reflects greater synchrony of activity within the central nervous system (CNS) during sleep (Greene and Frank 2010). SWA has been shown to parallel synaptic density (Feinberg and Campbell 2010) as well as increases in synaptic potentiation (Huber et al. 2004; Huber et al. 2006). Cellular, molecular, and neuromodulatory mechanisms, as well as changes in gene expression, all favor SWS, and specifically SWA, as a time for global synaptic downscaling (Tononi and Cirelli 2003, 2014) and synaptic plasticity (Chauvette et al. 2012) in the brain.

In contrast to the global neuronal deactivation of nREM sleep, during REM sleep, particular brain regions reactivate to levels similar to or exceeding those that occur during the wake state (Braun et al. 1997; Hobson et al. 1998). For example, visual association cortices as well as limbic and paralimbic structures (including the hippocampal formation, parahippocampal gyri, portions of the insula, the amygdala, and the anterior cingulate cortices) become reactivated (Maquet et al. 1996; Braun et al. 1997; Nofzinger et al. 1997; Braun et al. 1998). Conversely, the majority of the frontal association cortices remain inactivated from previous nREM sleep bouts (Braun et al. 1997; Lövblad et al. 1999). Given the limbic reactivation, most researchers support the notion that REM sleep is critical in selectively processing emotional memories (Maquet et al. 1996; Wagner et al. 2001; Hobson and Pace-Schott 2002; Nishida et al. 2009; Lara-Carrasco et al. 2009; Baran et al. 2012; Groch et al. 2013) or in processing motivational or reward-driven experiences (Nofzinger et al. 1997).

REM sleep is also characterized by muscle atonia and the titular rapid eye movements. The muscle atonia results from descending projections of the dorsolateral pontine reticular formation through the medulla and spinal cord to inhibit motor neurons (Hishikawa and Shimizu 1995). Waves generated in the pontine reticular formation that progress through the thalamic lateral geniculate body to the occipital cortex (PGO waves) play a major role in the endogenous visual system excitation characteristic of REM sleep (Callaway et al. 1987). Rhythmic activation of the vestibulo-oculomotor neurons leads to rapid eye movements (Pompeiano 1975; Hobson and Pace-Schott 2002), and the duration of PGO waves has been associated with duration of these eye movement events (Nelson et al. 1983). The endogenous activation of the extrastriate visual cortex in particular is associated with the visual elements of dreaming, another key feature of REM sleep (Braun et al. 1998; Hobson et al. 2000).

1.2.1.1 The Many Functions of Normal Human Sleep

As demonstrated by the dynamic brain activity during sleep, sleep also has dynamic functions. There are many theories as to why we sleep (Siegel 2005). Sleep plays a role in metabolic function (Morselli et al. 2011) as well as metabolite clearance from the CNS (Xie et al. 2013). The reduction in global neuronal firing rates during nREM

sleep has also been used to support the idea that sleep is a time for energy conservation (Berger 1975; Walker and Berger 1980; Berger and Phillips 1995). High levels of neuronal activation during REM sleep are not directly in line with this theory; however, it has been suggested that bouts of REM sleep may be necessary to maintain the CNS core temperature following reduced activation during nREM sleep (Wehr 1992). In addition, given that activation is reduced in a number of neurotransmitter systems during sleep, and during REM sleep specifically (e.g., noradrenaline, histamine, hypocretin, and serotonin), sleep may play an important role in resensitization of these neuronal circuits (Siegel and Rogawski 1988; Tsai et al. 1993; Hipólide et al. 1998, 2005; Pedrazzoli and Benedito 2004; Siegel 2005).

Sleep, and SWS in particular, has been implicated in immune system function and in immunological memory (Moldofsky et al. 1986; Redwine et al. 2000; Besedovsky et al. 2011). Growth hormone is also secreted during SWS (Takahashi et al. 1968; Honda et al. 1969; Sassin et al. 1969; Born et al. 1988; Marshall et al. 1996), which may indicate that sleep is an important part of growth and development. Lastly, as mentioned previously, a primary function of sleep is learning and memory (Stickgold 2005; Diekelmann and Born 2010). Importantly, these many possible outcomes of sleep are not mutually exclusive.

1.2.2 Sleep-Dependent Memory Consolidation in Young Adults

1.2.2.1 Declarative Memory

Memory consolidation, or the process through which a memory trace becomes more stable and less vulnerable to forgetting or interference, is greatest over sleep (Walker 2005; Stickgold 2005; Diekelmann et al. 2009; Diekelmann and Born 2010). Sleep-dependent memory consolidation (SDC) involves cellular and molecular changes, as well as changes at the systems level, to stabilize a particular memory for long-term recall and to integrate the memory into other existing memories.

In one of the earliest studies of memory consolidation over sleep, Jenkins and Dallenbach (1924) found that memory for nonsense syllables was greater following bouts of sleep than following bouts of wake. Since then, the role of sleep on declarative memory has been more thoroughly investigated, and many studies have replicated the improved recall following sleep (Gais and Born 2004a). For example, when individuals were taught a list of semantically unrelated word-pairs either in the morning or in the evening, recall accuracy was significantly greater 12 h later when the intervening interval contained sleep (e.g., Donohue and Spencer 2011; Wilson et al. 2012). These results suggest that during sleep, memories are actively consolidated, leading to a reduction in forgetting and more long-term retention of the encoded information (Ellenbogen et al. 2006).

Particular sleep stages appear to play different roles in memory consolidation in adults (Spencer 2013). For example, SDC of declarative memory is often associated

with time spent in SWS (Gais and Born 2004a, b). Specifically, replay of activation patterns in the hippocampus (Pavlides and Winson 1989) during SWS may be critical to the consolidation of declarative memories (Wilson and McNaughton 1994). Hippocampal replay during early bouts of SWS is observed directly following new learning in rats (Wilson and McNaughton 1994; Skaggs and McNaughton 1996; Louie and Wilson 2001; Ji and Wilson 2007). Similarly, a study by Peigneux et al. (2004) showed that neurological activation within the hippocampus during learning of a new declarative task in young adults was mirrored in a subsequent bout of SWS. Importantly, the reactivation of the hippocampus during SWS was specifically associated with improved performance on this declarative memory task upon waking. Reduced acetylcholine levels in the hippocampus during SWS appear to allow for hippocampal replay, and is necessary for declarative memory consolidation, but not for non-declarative memory consolidation (Gais and Born 2004b).

Targeted experimental reactivation of hippocampal neuronal networks has also been shown to improve declarative memory. During encoding, declarative items were paired with either olfactory (Rasch et al. 2007; Barnes and Wilson 2014) or auditory (Rudoy et al. 2009; Cairney et al. 2014a) stimuli. During subsequent SWS, a subset of the sensory stimuli was presented to the participant. Memory retention for the reactivated items was significantly improved compared to the items that were not cued during sleep.

REM sleep may also play a role in the consolidation of declarative information. Whereas SWS is necessary for initial phases of consolidation, neocortical activation of the hippocampus during REM sleep may reflect a later stage of memory consolidation (Datta 2000; Louie and Wilson 2001; Jones and Wilson 2005). REM sleep has been suggested to be involved in reorganization, integration, and optimization of previously learned material (Laureys et al. 2001; Peigneux et al. 2003; Walker and Stickgold 2010), as well as the integration of unassociated information into currently existing networks, thus enhancing creative problem-solving (Cai et al. 2009). REM sleep may also potentially be a time in which older memory traces are intentionally weakened (Poe et al. 2000), thereby making memory recall more efficient.

1.2.2.2 Procedural Memory

Procedural memories have also been shown to be enhanced over sleep in young adults (Plihal and Born 1997; Fischer et al. 2002; Walker et al. 2005; Wilson et al. 2012). REM sleep has been proposed to play a role in the consolidation of procedural memories (Karni et al. 1994; Plihal and Born 1997; Maquet et al. 2000; Laureys et al. 2001; Smith et al. 2004), although this has been debated (Siegel 2001; Rasch et al. 2009; Laventure et al. 2016). Alternatively, nREM2 sleep and sleep spindles during nREM2 have also been associated with procedural memory consolidation (Smith and MacNeill 1994; Walker et al. 2002; Fogel and Smith 2006; Nishida and Walker 2007; Fogel et al. 2007b; Laventure et al. 2016). It is possible that both nREM and REM sleep contribute to procedural learning, but in different capacities (Stickgold et al. 2000; Smith et al. 2004; Fogel et al. 2015).

In conjunction with the sleep stage discrepancies, the functional role of sleep in procedural memory consolidation is also still controversial (Song et al. 2007; Rickard et al. 2008; Cai and Rickard 2009; Albouy et al. 2013). Recent studies have questioned the magnitude of the effect of sleep on procedural memory (Pereira et al. 2015), as well as whether additional features, such as explicit awareness during procedural learning (Robertson et al. 2004), modify the influence of sleep. Further, the time course of sleep with respect to learning (Brawn et al. 2010) may also factor into the possible benefits of sleep on procedural memory consolidation.

1.2.2.3 Emotional Memory

Emotional memory consolidation has also been shown to benefit from sleep (Wagner et al. 2001; Hu et al. 2006; Holland and Lewis 2007; Sterpenich et al. 2007; Payne et al. 2008; Payne and Kensinger 2010; Lewis et al. 2011; Baran et al. 2012; Deliens et al. 2014). Sleep prioritizes the consolidation of emotional elements of stimuli above more neutral information in the background (Payne et al. 2008). In addition, Baran and colleagues demonstrated that the emotional reactivity to stimuli is protected over sleep (2012). When memory for emotional stimuli was probed after a delay, the strength of neuronal activation and the functional connectivity between cortical networks (especially the medial prefrontal cortex (mPFC)) and the hippocampus were stronger for emotional compared to neutral stimuli (Sterpenich et al. 2007). This relationship was especially observed when sleep followed encoding compared to wake. The mPFC is thought to provide top-down inhibitory control over the amygdala, thus maintaining control of the emotional response (Ochsner and Gross 2005). Sleep has been shown to depotentiate amygdala reactivity to emotional stimuli (van der Helm et al. 2011), whereas sleep deprivation has been shown to reduce the functional connectivity between the mPFC and the amygdala (Yoo et al. 2007). The result of sleep deprivation is thus an inappropriate hyperarousal of the limbic system to emotional stimuli. Sleep-related changes in emotional memory recall, as well as the underlying neurological changes in connectivity, were also shown to be incredibly long-lasting (Wagner et al. 2006; Sterpenich et al. 2009).

A number of studies have supported the role of REM sleep in both emotional processing (Lara-Carrasco et al. 2009; Baran et al. 2012) and emotional memory consolidation (Wagner et al. 2001; Nishida et al. 2009; Groch et al. 2013). During REM sleep, the amygdala, hippocampus, and cortical areas show a distribution of activation which may support a REM sleep benefit on emotion processing (Maquet et al. 1996). Similarly, theta coherence between the amygdala, the mPFC, and the hippocampus during REM sleep was selectively correlated to changes in fear memory in rats (Popa et al. 2010). However, not all research supports a functional role of REM sleep in emotional SDC. For example, in one study, REM sleep deprivation was demonstrated to have no impact on SDC of emotional memories (Morgenthaler et al. 2014).

Recent work has also attributed emotional SDC to SWS. Groch and colleagues suggest that phasic noradrenergic activity in early bouts of SWS supports the

consolidation of memories that require both hippocampal and amygdala activation (2011). Hippocampal-based fear contextual memory was stabilized during SWS in mice due to CA1 network stabilization (Ognjanovski et al. 2014). In humans, targeted memory reactivation using auditory cues during SWS was shown to enhance memory recall for emotional memories (Cairney et al. 2014a). In another study, overnight SWA was pharmacologically enhanced following the encoding of an emotional text. Significant memory improvements were observed in the group with increased SWA compared to the control group (Benedict et al. 2009). Similarly to procedural memory consolidation, new research is supporting a role for multiple sleep stages in the progression of emotional memory consolidation (Cairney et al. 2014b).

Likewise, the cycling between nREM and REM sleep stages may reflect a sequential pattern of consolidation. In rodent studies, nREM sleep is important for early stages of memory consolidation, whereas REM is needed for later stages of consolidation (Giuditta et al. 1995; Louie and Wilson 2001; Ambrosini and Giuditta 2001). A recent study using transgenic mouse models has shown that REM sleep may enhance SWA in the subsequent nREM bout, thereby subsequently enhancing synaptic plasticity indirectly (Kashiwagi and Hayashi 2016). In human research, the sequential relationship between nREM and REM sleep has also been implicated in memory consolidation (Ficca et al. 2000b; Griessenberger et al. 2012; Grosmark et al. 2012; Spencer 2013; Sonni and Spencer 2015).

1.2.3 Summary

A number of studies have supported sleep as a time in which memory consolidation occurs in young adults. Specifically, nREM sleep, and accompanying elements such as slow oscillations, SWA, and sleep spindles, is associated with synaptic plasticity and with the transfer of information from hippocampal to neocortical networks. Importantly, new work is investigating the relationship between nREM and REM sleep with respect to memory processing. Sleep has been shown to improve memory in declarative, procedural, and emotional realms, although the procedural memory literature is inconsistent. Therefore, young adult SDC will be a foundation from which to compare other developmental life stages.

1.3 Prenatal Development and Infancy

1.3.1 Fetal and Infant Sleep

Sleep first develops between 26 and 28 weeks gestational age (Graven and Browne 2008). Early in development, adult-like sleep stages cannot be distinguished. At approximately 30 weeks gestational age, sleep is first differentiated into quiet and active sleep (de Weerd and van den Bossche 2003). Quiet sleep is identifiable by

delta waves and *tracé alternant* patterns of brain activity. *Tracé alternant* are bursts of slow waves intermixed with sharp waves, with alternating periods of quiescence. As such, quiet sleep is considered an immature form of adult nREM sleep. Alternatively, active sleep is identifiable by variability in respiration and heart rate with both slow and rapid eye movements; active sleep is therefore considered to be an immature form of adult REM sleep (Prechtl 1974). Rapid eye movements are first observable at 30 weeks gestational age, and increase through approximately 40 weeks, after which the rate of eye movements declines (Bots et al. 1981; Birnholz 1981; Inoue et al. 1986; Okai et al. 1992). Data from prematurely born infants has supported this pattern of eye movements increasing between 30 and 41 weeks postconceptional age (Dreyfus-Brisac 1970; Petre-Quadens and De Lee 1974). By 47 weeks gestational age, sleep stages can be differentiated into the standard adult stages as the *tracé alternant* are replaced with increasing slow waves (Sterman et al. 1977; Dan and Boyd 2006).

In neonates, sleep accounts for approximately 16–18 h of the day. Neonatal sleep is quite fragmented, alternating rapidly between the active and quiet sleep stages, and with more frequent transitions from sleep to wake (Anders and Roffwarg 1973; Peirano and Algarín 2007). As the forebrain develops, greater control is gained over sleep and waking states (Mirmiran et al. 2003); at 2 weeks of age, neonates are only capable of remaining asleep for 4 h at a time. By the end of the 1st year of life, an infant can remain sleeping without awakening for 7 h (Anders and Keener 1985). Sleep also begins to be consolidated to nocturnal bouts with a reduction in diurnal sleep, and by the end of the 1st year, total sleep time in infants is reduced to about 14 h (Iglowstein et al. 2003).

Characteristic features of the sleep EEG also begin to emerge in the 1st year of life. Sleep spindles are first identifiable around 8 weeks post-gestational age (Metcalf 1969, 1970; Tanguay et al. 1975; Jenni et al. 2004). In the first 6 months of life, spindle density (number of spindles per minute nREM sleep) rapidly increases, spindle amplitude increases, and spindle duration decreases (Tanguay et al. 1975). These changes in spindle architecture are thought to reflect the maturation of the physiological system that produces spindles, including thalamocortical networks, as well as the growth of dendrites and the myelination of neurons.

In concordance with the progressive maturation of the brain, prominent changes in active/REM sleep occur. In newborns, active sleep is entered directly from wakefulness; after the first few months, however, quiet sleep predominates early in the sleep bout, whereas active sleep becomes more prominent later in the sleep bout. This distribution is more in line with adult sleep patterns. The proportion of REM or active sleep across the night also changes, comprising 50% of the night in newborns (Anders and Keener 1985) and decreasing throughout the life span (Ficca et al. 2000a).

The extremely large proportion of REM sleep in early development is thought to play a role in brain maturation. Roffwarg et al. proposed that REM sleep was necessary for CNS development (1966). They suggested that since exogenous activation of the nervous system is limited in utero due to the fetus spending limited time in an awake state, REM sleep was necessary to supply sufficient endogenous

neuronal activation to encourage development. Many studies have supported this hypothesis (Mirmiran et al. 1983a, 2003; Van Someren et al. 1990). For example, pharmacologically or instrumentally suppressing REM sleep for the first few weeks of life resulted in significantly reduced regional brain weights of the cerebral cortex and the medulla oblongata in rat pups (Mirmiran et al. 1983a). However, with further research, the ontogenetic hypothesis has been modified to demonstrate that REM sleep does more than simply mimic the wake state. Suppression of REM sleep in kittens significantly enhanced brain deterioration from monocular deprivation, despite the fact that REM sleep was replaced primarily by active wake (Marks et al. 1995). Further, more recent work has suggested that early REM/active sleep specifically reduces apoptosis during brain maturation (Morrissey et al. 2004). Thus, as the progression of CNS development is reduced with age (Dobbing and Sands 1973), so is the need for REM sleep.

Parallel to the decrease in REM sleep is an increase in SWA across early development. The intensification of SWA has been suggested to reflect the increase in synaptogenesis and synaptic connectivity associated with brain maturation (Frank et al. 2001; Fattinger et al. 2014; Huber and Born 2014). In addition, SWA has been associated with learning and memory consolidation throughout the life span given its relationship to synaptic plasticity (Huber et al. 2004). Important to note is that theta activity (6.5–9 Hz), and not SWA (as in adults; Tononi and Cirelli 2006), appears to indicate sleep pressure in infants (Jenni et al. 2004). In a longitudinal study of nocturnal EEG in human infants, Jenni and colleagues demonstrated that theta activity declined over successive quiet sleep/nREM bouts. At 9 months of age, this decline approached an exponential function, reflecting a dissipation of sleep tendency over consecutive bouts.

Overall, the prominent changes in sleep throughout infancy seem to reflect the drastic maturation of the CNS. Developmental changes in SWA, sleep spindles, and REM sleep are associated with neuronal plasticity, synaptic efficiency, and synaptic proliferation. Given these relationships, it seems likely that sleep would play a pronounced role in SDC in infants.

1.3.2 Sleep-Dependent Memory Consolidation in Infants

As sleep changes so dramatically across infancy, it is difficult to associate any particular component of sleep with specific behavioral changes. In addition, research paradigms for infant memory are often limited by the fact that this population lacks strong verbal communication skills. However, learning and cognition have been associated with sleep in infancy. For example, neonates have been shown to learn during sleep. Adaptation to a conditioned response can be achieved while the newborn is sleeping (Fifer et al. 2010; Reeb-Sutherland et al. 2011). This response may be sleep stage dependent, as work in rats showed that classical conditioning during sleep was only achieved during REM, and not nREM sleep (Mirmiran et al. 1983b). Although in line with the ontogenetic hypothesis of REM sleep, these results

may suggest an additional benefit to the high prevalence of REM in early development given the adaptive benefit of learning during sleep.

Infant sleep habits have also been associated with learning and memory that occurs during wakefulness. Habitual nap duration and nocturnal sleep efficiency as determined by parental questionnaires were associated with improved generalization on an imitation task (Lukowski and Milojevich 2013). Similarly, nighttime sleep quality variables, such as sleep efficiency, were positively correlated with memory encoding in 6-month-old children (Konrad et al. 2016a). In this study, sleep quality measures obtained from 24-h actigraphy recordings were associated with performance on an immediate imitation task. This relationship was not observed in 12-month-old children, however.

1.3.2.1 Declarative Memory

Very few studies have assessed the role of infant sleep on declarative memory consolidation. These studies have also only focused on napping, rather than nocturnal sleep in infants. A benefit of sleep on declarative memory in infants was first demonstrated in a study by Seehagen and colleagues (2015). Following observation of novel behavioral actions with a puppet by experimenters, 6- and 12-month-old infants either napped (nap group) or napped less than 30 min (no-nap group) during a 4-h delay. Following this delay, only infants in the nap group showed significant imitation of the novel actions. Further, following a 24-h delay, the nap condition showed significantly more memory for the actions than the no-nap group.

The Seehagen study is somewhat contradictory to earlier studies on artificial language learning infants. In 15-month-old infants, veridical memory for word strings of an artificial language was not better following a nap, and in fact wake seemed to benefit recall after a 4-h delay. However, napping infants showed a greater abstraction of grammar rules with sleep (Gómez et al. 2006), and this effect was long-lasting, whereas the wake benefit of veridical word recall was not (Hupbach et al. 2009). These studies are difficult to interpret with respect to the role of sleep in declarative memory consolidation in infants. The wake benefit on initial veridical recall, although not a lasting effect, would suggest that sleep does not benefit declarative memory performance. However, the sleep benefit for rule abstraction is important in language learning contexts in particular.

Recent work has further investigated the role of infant sleep on abstraction and generalization. Infants between the ages of 9 and 16 months encoded objects with both specific and general categorical word meanings (Friedrich et al. 2015). Results suggest that napping maintains memory for specific, veridical word meanings while additionally abstracting categorical information. Further, the observed semantic generalization was associated with sleep spindles during the nap. In two studies of deferred imitation, napping in 12-month-old infants was also associated with both veridical recall and generalization of the demonstrated hand puppet actions to novel puppets (Konrad et al. 2016b, c).

1.3.2.2 Procedural Memory

Only one study has investigated the role of sleep on procedural-type memory consolidation in infancy. Three-month-old infants were trained to activate a mobile over their crib with foot kicking behavior. Two weeks later, after induced forgetting had occurred, this memory was reactivated. Duration of sleep following this reactivation was positively associated with recall of the behavior (Fagen and Rovee-Collier 1983). This suggests that memory for procedural information is benefited by sleep in infancy, although the evidence is minimal and warrants additional examination.

1.3.2.3 Emotional Memory

To date, there have been no studies assessing emotional memory consolidation across sleep in infants.

1.3.3 Summary

In sum, the research on SDC in infancy is limited and somewhat contrary. Additional research is needed to replicate current findings and to help better understand the cognitive functions of sleep during this time. Specifically, more research is needed to better understand how physiological differences in sleep are related to changes in the memory consolidation process. To date, no research has examined nocturnal sleep in infants nor emotional memory consolidation in infants. Given the higher proportion of REM sleep during infancy, research on memory consolidation across both the emotional and procedural domains is especially warranted.

1.4 Early Childhood

1.4.1 Early Childhood Sleep

Sleep continues to evolve throughout childhood. Total sleep time declines steadily. At 2 years of age, most children sleep between 10 and 15 h across a 24-h period. By 12 years of age, total sleep time drops to between 8 and 10 h (Iglowstein et al. 2003). One of the most obvious sleep-related changes during early childhood is the diminishment of napping. On average, children shift from two midday naps to only one midday nap at about 18 months. Children will transition to a monophasic sleep pattern (only sleeping at night) during the preschool age range (~3 to 5 years;

Weissbluth 1995; Jenni and Carskadon 2007). The likelihood of napping decreases from 50% in 3-year-olds to only about 1% in 7-year-olds (Iglowstein et al. 2003).

It is probable that the reduction in diurnal sleep across development reflects brain maturation (Lam et al. 2011). During early childhood, synaptic thresholds may be reached faster than adults due to less efficient and more synaptically dense neuronal networks (Huttenlocher 1979; Feinberg et al. 1985; Huttenlocher and Dabholkar 1997). As such, children need a period of global downscaling during the day. Almost 50% of the total naptime for a preschool-aged child is dedicated to SWS (Kurdziel et al. 2013), further supporting that the nap is a time for synaptic downscaling. However, as cortical networks develop, the need for the nap decreases until sleep is consolidated to one nocturnal bout.

In line with the changes in sleep pattern are additional changes in sleep physiology. REM sleep continues to decline, reaching the adult proportions (~20% of the night) by approximately 10 years of age (McCarley 2007). Interestingly, REM sleep is relatively lacking during daytime naps in preschool-aged children (Kurdziel et al. 2013). SWA also continues to increase throughout development (Ohayon et al. 2004; McCarley 2007; Kurth et al. 2010). The maturation of delta waves has been shown to mimic the progression of synaptic density and metabolic activity specifically in the frontal cortex (Feinberg et al. 1990). In addition, maturation of specific regions of the cortex has been associated with increases in localized SWA, as well as development of regional-specific cognitive abilities (Kurth et al. 2012). This work further supports that SWA may be used as a measure of cortical maturation (Feinberg et al. 1990; McCarley 2007; Kurth et al. 2012).

An increase in nREM2 sleep is also observed, and sleep spindles continue to mature, throughout childhood. Spindles decrease throughout the 2nd year of life but return to average adult frequency levels within the preschool years (Tanguay et al. 1975). Sleep spindles in early childhood may reflect plasticity and new learning, as in adults (Kurdziel et al. 2013). However, it is also possible that spindle measures reflect more trait-like differences between individuals. For example, in school-aged children, sigma power was positively associated with IQ (Geiger et al. 2011), and spindle density was associated with narrative memory differences in a standardized assessment (Chatburn et al. 2013).

1.4.2 Sleep-Dependent Memory Consolidation in Children

1.4.2.1 Declarative Memory

Like infancy, early childhood is a tentatively explored age range with respect to SDC. Only recently has early childhood been a targeted population for sleep research. Within the declarative domain, the literature supports SDC in children. Some of the first childhood-specific examples of SDC in declarative tasks demonstrate that both 6–8-year-old and 9–12-year-old children recall significantly more word-pairs following a period of nocturnal sleep than following a period of wake

(Backhaus et al. 2008; Wilhelm et al. 2008). Children have also been demonstrated to gain a benefit of nocturnal sleep (Wilhelm et al. 2008; Henderson et al. 2012) or diurnal sleep (napping; Kurdziel et al. 2013) on a declarative 2D object-location task. Specifically, improved declarative memory was associated with sleep spindles in the nap, and this nap benefit remained even following subsequent overnight sleep (Kurdziel et al. 2013).

There have been a number of studies examining the role of sleep in vocabulary learning – an important goal of early childhood education (Axelsson et al. 2016). Williams and Horst (2014) showed that when a nap directly followed learning of new vocabulary words through a storybook, there were significant and sustained improvements in word identification in 3-year-old children. The function of sleep in vocabulary learning has also been examined in a slightly older (7–12 years of age) developmental population (Henderson et al. 2012). Across all measures, sleep was shown to improve retention of new words and led to the incorporation of these words into the children's lexicon.

1.4.2.2 Procedural Memory

Similarly to adults, SDC in the procedural domain during childhood is inconsistent. Children between the ages of 6 and 13 showed no benefit of nocturnal sleep on a serial reaction time task (SRTT; Fischer et al. 2007; Henderson et al. 2012), a task of procedural skill that has been shown to elicit a sleep benefit adults (Walker et al. 2002; Fischer et al. 2002; Korman et al. 2007; Schönauer et al. 2013). One study even showed a wake benefit on the SRTT in children (Wilhelm et al. 2008).

It has been suggested that sleep in children prioritizes consolidation of explicit or more hippocampal-based tasks. This theory has been supported by recent research within the procedural realm. In one experiment, 4–6-year-old children were given extensive training on a sequencing task across 3 days, prior to being assessed for performance improvements across a nap. With this additional training, children were able to show nap-dependent improvements in motor performance (Wilhelm et al. 2012). It was posited that the prioritized explicit knowledge was consolidated across the intervening periods of nocturnal sleep between training sessions, thus allowing for the consolidation of implicit information across the latter nap. Similarly, nap-dependent performance improvements on a modified SRTT task were observed in preschool-aged children, but only following additional overnight sleep (Desrochers et al. 2016). In this study, explicit recall of the implicitly learned motor sequence was also significantly greater when a nap followed encoding compared to equivalent wake. Sleep-dependent prioritization for explicit procedural information has also been demonstrated in adults (Robertson et al. 2004). However, when both children and adults were taught a task implicitly, children demonstrated greater explicit knowledge of the task than adults (Wilhelm et al. 2013).

Additionally, work in children with attention deficit hyperactivity disorder (ADHD) supports the preferential consolidation of explicit features of procedural tasks over sleep. Children with ADHD have hypoactivation of the prefrontal cortex,

leading to impairment of explicit declarative memory consolidation (Prehn-Kristensen et al. 2011a). Compared to healthy controls, children (9–12 years of age) showed SDC of an implicit procedural sequential button-pressing task. It was suggested that due to reduced explicit consolidation in this population, children with ADHD have reduced implicit-explicit competition during overnight sleep and are therefore able to demonstrate implicit SDC (Prehn-Kristensen et al. 2011b).

The hypothesis that children prioritize explicit, hippocampal-dependent features of new information for consolidation is supported by their sleep architecture. Children have significantly greater amounts of SWS (Ohayon et al. 2004) and have greater spectral power in SWA compared to adults (Kurth et al. 2010). SWS and SWA have been associated with hippocampal activation (Moroni et al. 2007; Dang-Vu et al. 2008) as well as consolidation of hippocampal-dependent tasks in adults (e.g., Peigneux et al. 2004). Children's ability to extract the explicit information from a procedural sequencing task over sleep was significantly correlated with SWS, and SWA (Wilhelm et al. 2013), especially within the range of slow oscillations (<1 Hz). Additionally, explicit extraction in children was shown to be associated left hippocampal activation (Wilhelm et al. 2013). Lastly, children with ADHD demonstrated SDC of an implicit procedural task (Prehn-Kristensen et al. 2011b); however, while slow oscillations were associated with declarative memory SDC in healthy controls, this association was not observed in the ADHD population (Prehn-Kristensen et al. 2011a). Thus, the large proportion of sleep dedicated to SWS in children, including during diurnal sleep bouts, may be associated with increased hippocampal-dependent learning.

1.4.2.3 Emotional Memory

In children, SDC has also been examined with respect to emotional memories. Healthy children between the ages of 9 and 12 remember significantly more images overall following sleep than following wake; further, they were shown to preferentially consolidate emotionally valenced images compared to neutral images (Prehn-Kristensen et al. 2013). Consolidation of emotional images in children was associated with nREM sleep, the spectral power of the slow oscillation, and theta oscillations during REM sleep (Prehn-Kristensen et al. 2013). Therefore, emotional memory consolidation in children appears to require an interplay between nREM and REM sleep, similarly to adults. More research is needed to better understand the relationship between sleep physiology and emotional memory consolidation in children.

1.4.3 Summary

Overall, work in early childhood supports a relationship between sleep and memory consolidation. Primarily, the high proportion of SWS, and the increased SWA across

nREM sleep bouts, fosters the consolidation of explicit information and of hippocampal-based memories. This was shown to be consistent across all memory domains. Important to note, however, is that the designation of "childhood" encompasses a huge range of neurological development and accompanying changes in learning capacity. Therefore while the current research supports SDC across childhood, there are many ages and developmental stages within this population that have not been investigated.

1.5 Adolescence

1.5.1 Adolescent Sleep

Following the onset of puberty, a number of physiological and neurological changes occur. Sleep is not spared from these pubertal alterations. Total sleep time declines from the prepubertal ~10 h to the more adult-like 8 h by 16 years of age (Iglowstein et al. 2003). The timing of sleep also changes. As children progress through pubertal stages, their chronotypes shift to more evening-type "night owls" as opposed to the morning-type "early birds." Adolescents tend to fall asleep and wake up later due to a later plasma melatonin offset with age and pubertal stage (Carskadon 1990).

The physiology of sleep changes with adolescence as well. REM sleep duration increases only slightly across adolescence, but still significantly (Feinberg et al. 2012). In addition, theta power in both REM and nREM sleep stages declines (Feinberg and Campbell 2013). The most prominent change in sleep architecture is the reduction of SWS. There is a 40% decline in SWS from prepubertal to mature stages of development, with a corresponding increase in nREM2 (~20%; Jenni and Carskadon 2004). Accompanying this is a decline in SWA (Gaudreau et al. 2001; Jenni and Carskadon 2004; Feinberg and Campbell 2010, 2013). Importantly, however, despite a global reduction in SWA in more mature adolescents, the typical decline of SWA over the course of the night is still observed; therefore, despite reduced spectral power, SWA in the adolescent is functioning to reduce sleep pressure similarly to children and adults (Jenni and Carskadon 2004; Campbell et al. 2011).

The reduction in SWA across adolescence, compared to the marked increase from infancy through childhood, is thought to reflect changes in synaptic connectivity. Postnatal development of neuronal connections leads to increases in SWA (Feinberg and Campbell 2013); however, starting in early adolescence, dramatic pruning of synapses occurs, such that synaptic density at 20 years of age is half what it was at 10 years (Huttenlocher 1979). Therefore it follows that SWA would decline in parallel.

1.5.2 Adolescent Sleep-Dependent Memory Consolidation

Given the vast restructuring of the CNS throughout adolescence, and the relationship between sleep and synaptic pruning, adolescence is an interesting population in which to study SDC. However, very few studies have addressed the relationship between sleep and memory in this age group. Difficulties with studying the role of SDC in adolescence include the variation in pubertal onset for genders (Sisk and Foster 2004), as well as the need to consider the effects of hormonal fluctuations on memory and attention (Sherwin 2012). Nevertheless, SDC in adolescence has begun to receive greater attention in the literature.

1.5.2.1 Declarative Memory

The majority of SDC research in adolescence examines declarative memory consolidation. For example, 17-year-old German high school students displayed significantly enhanced memory for English translations of German words when sleep directly followed learning compared to a 12-h period of wake (Gais et al. 2006). Similarly, using the paired-associates test of declarative memory, Potkin and Bunney (2012) demonstrated a sleep benefit for adolescents between 10 and 14 years of age. Naps in schools were shown to significantly improve retention of declarative information taught in a classroom setting, whereas significant decay was observed without daytime napping (Lemos et al. 2014).

However, not all studies demonstrate a benefit of sleep on declarative memories in adolescence. Holz et al. (2012) showed that performance on a word-pair test was actually better the following morning when a long delay (7.5 h) of wake followed encoding, compared to when encoding occurred directly prior to sleep. Importantly, this effect was not maintained 1 week later. In a different study, no significant sleep benefit was found across a ~50 min nap compared to either a period of activity or passive rest in 16-year-old females; however, performance on the word-pair learning task was significantly correlated with sigma power, suggesting some level of active consolidation over sleep (Piosczyk et al. 2013).

The discrepancies in declarative SDC across adolescence are likely related to the changes in SWS and in the vast restructuring of the brain. Hypoactivation of the prefrontal cortex in ADHD has been shown to reduce declarative SDC in 10–16-year-olds. This reduction in SDC was associated with a dysfunctional slow oscillation in individuals with ADHD. Experimentally increasing the slow oscillation during early SWS through transcranial oscillating direct current stimulation leads to observed improvements in declarative memory consolidation in 10–14-year-olds (Prehn-Kristensen et al. 2014).

1.5.2.2 Procedural Memory

Very few studies have examined SDC of procedural memory in adolescence. In one study, individuals (10–13 years) were taught the procedural task of mirror tracing either in the morning (wake group) or the evening (sleep group). Speed and accuracy at the retrieval period 12 h later were significantly better than during encoding; however, there were no differences between the sleep and wake groups (Prehn-Kristensen et al. 2009). Importantly, the age group tested were early adolescents, encompassing a predominantly prepubertal age range. In a separate study, older adolescents (16–17 years) exhibited significant improvements on a procedural finger tapping task when trained directly prior to sleep, as opposed to 7.5 h prior to sleep. This benefit was long-lasting, remaining for at least 7 days after initial learning (Holz et al. 2012). Therefore, it is possible that SDC of procedural memory in adolescence is dependent on structural neuronal changes that occur throughout puberty.

1.5.2.3 Emotional Memory

Emotional declarative memories have also been examined, albeit rarely, with respect to SDC in adolescence. Following sleep, 10–13-year-olds were better at recognizing pictures from the International Affective Picture System (IAPS; Lang et al. 2008) than following an equivalent period spent awake (Prehn-Kristensen et al. 2009; Prehn-Kristensen et al. 2011a). Memory was greater for emotional (negative) compared to neutral pictures, and performance across sleep was significantly associated with slow oscillation power during nREM sleep (Prehn-Kristensen et al. 2011a). Again, it is important to note that the individuals in these studies were in early adolescence.

1.5.2.4 Sleep-Dependent Memory Consolidation Following Sleep Restriction

Given the later sleep onset in adolescence, but the requirement for early rise times for school attendance, many adolescents are experiencing sleep deprivation over the course of the week (Carskadon 2011). As such, there have been a number of studies examining the role of restricted sleep on memory consolidation in adolescence. For example, Kopasz and colleagues (2010) had 14- to 16-year-olds learn a paired-associate task after which they were sleep restricted (4-h night sleep opportunity) or not (9-h sleep opportunity) at night. After a recovery night, memory performance was assessed. No significant group differences were observed in memory recall performance. This result is possibly due to the lack of a difference in time spent in SWS between the experimental conditions. However, in the sleep deprivation group, performance was significantly correlated with the percentage of nREM sleep across the recovery night, whereas performance did not correlate with any measure of sleep architecture for the control group.

In a similar experiment, adolescents that experienced 4 days of sleep restriction did not significantly differ from controls on either a declarative (word-pair) or a procedural (mirror tracing) memory task. Interestingly, time spent in SWS remained constant across sleep restriction conditions, whereas REM sleep declined with restriction. The percentage of time spent in SWS therefore *increased* with decreased sleep time. This suggests that, during adolescence, SWS is conserved despite sleep restriction (Voderholzer et al. 2011).

1.5.3 Summary

Overall, there is clear evidence of SDC in adolescence. However, SDC of procedural and declarative information is inconsistent and may depend on pubertal status. Across the developmental trajectory into adulthood, there seems to be a clear bias of SDC toward declarative information. This may be due to the rapidly increasing power of SWA or to the large percentage of time spent in SWS. Intriguingly, even across multiple nights of sleep deprivation, adolescents were shown to conserve SWS time at the expense of other sleep stages (REM in particular).

Following puberty, however, there are drastic reductions in synaptic density and a resultant parallel reduction in SWA. It is at this point in development where procedural SDC gains more equal footing with declarative SDC. Thus, puberty may be the transition point in which prioritization of hippocampus-dependent, explicit information is diminished. However, further research is needed to examine the interplay between these memory systems across development and the associated role of sleep in these domains.

1.6 Middle-Aged and Older Adulthood

1.6.1 Middle-Aged and Older Adult Sleep

As adults age, they tend to go to bed earlier and wake up earlier, showing a shift toward morning chronotypes. Sleep quality also declines with age (Carrier et al. 1997). Total sleep time decreases, sleep efficiency is reduced, and sleep becomes more fragmented. These changes in sleep time are associated with reductions in health (Newman et al. 1997). In older adults both too short and too long of sleep durations were associated with increased mortality risk (Dew et al. 2003; Gangwisch et al. 2008), whereas the same was not true for middle-aged adults (Gangwisch et al. 2008). Age-related changes in sleep time have also been associated with diabetes mellitus and impaired glucose tolerance (Gottlieb et al. 2005; Yaggi et al. 2006), hypertension (Gangwisch et al. 2006; Gottlieb et al. 2006), and coronary heart disease (Ayas et al. 2003). Interestingly, older adults appear to have a higher tolerance for sleep deprivation than younger adults (Buysse et al. 1993; Stenuit

and Kerkhofs 2005; Bliese et al. 2006; Duffy et al. 2009). It has been suggested that these age-related changes in sleep time might be due to the reduced cell numbers in the ventrolateral preoptic nucleus (VLPO) of the hypothalamus in older adults (Hofman and Swaab 1989; Gaus et al. 2002; Duffy et al. 2009). The VLPO inhibits monoaminergic arousal systems thereby allowing for the transition to sleep from wakefulness (Gaus et al. 2002; Fuller et al. 2006).

Sleep architecture also changes with age. The most dramatic change in sleep architecture is the decline in SWS (Hirshkowitz et al. 1992; Bliwise 1993; Carrier et al. 1997; Ohayon et al. 2004; Cooke and Ancoli-Israel 2011). In a study of adult men, SWS decreased from 18.9% in young adulthood to 3.4% in middle-aged adulthood (up to 50 years of age; Van Cauter et al. 2000). The reduction in SWS time and the fragmentation of SWS in the elderly have been shown to correlate with levels of amyloid beta in the cerebral spinal fluid (Varga et al. 2016b). This supports that SWS functions to clear neuronal metabolites and implicates sleep changes in age-related health risks.

The percentage of the night spent in REM sleep declines with age, although this decline parallels the reduction in sleep time. SWS and REM sleep reductions are compensated by increases in nREM1 sleep and awakenings, whereas nREM2 stays fairly consistent throughout aging (Hirshkowitz et al. 1992; Bliwise 1993; Carrier et al. 1997; Van Cauter et al. 2000; Ohayon et al. 2004; Cooke and Ancoli-Israel 2011; Spencer 2013). As sleep quality declines, there is a corresponding increase in daytime sleepiness with age (Ancoli-Israel 1997). This suggests that age does not diminish sleep need (Duffy et al. 2009). The age-related decline of sleep is thought to be related to disruption of circadian rhythms or to medical causes such as sleep disorders or prescribed medications (Ancoli-Israel 1997; Cooke and Ancoli-Israel 2011).

SWA has also been shown to continue to decrease throughout middle-aged and older adulthood (Landolt et al. 1996; Carrier et al. 2001; Gaudreau et al. 2001). The reduction in SWS and SWA is attributed to progressive atrophy of the mPFC (Mander et al. 2013; Varga et al. 2016a), as well as to reductions in growth hormone with age (Van Cauter et al. 2000). In addition, the progressive decline in SWA across the night is reduced in middle-aged adulthood, suggesting a reduction of homeostatic sleep pressure (Landolt et al. 1996; Carrier et al. 2001; Gaudreau et al. 2001; Darchia et al. 2007). In young adults, sleep spindles typically increase over the course of the night, but this is also attenuated in older adults (Landolt et al. 1996).

Theta and sigma power have also been shown to decrease with age (Landolt and Borbély 2001; Carrier et al. 2001; Gaudreau et al. 2001). Age-related reductions in spectral power are most pronounced in the frontal regions of the brain (Landolt and Borbély 2001). These global reductions in oscillatory power, especially those in nREM sleep, likely reduce synaptic plasticity within the aging brain; thus, there is strong reason to predict that SDC in middle-aged and older adults is impaired (Fogel et al. 2012).

1.6.2 Sleep-Dependent Memory Consolidation in Middle-Aged and Older Adults

Decline in memory is one of the greatest fears in older adults. Yet often the perceived memory loss is not representative of the actual decline in memory capabilities in healthy aging (Bolla et al. 1991). There is neurobiological reason to suspect a decline in cognitive abilities with age. Age-related changes are most prominent in prefrontal gray matter, with smaller degradations in the fusiform, inferior temporal, and superior parietal cortices (Raz et al. 1997). Interestingly, only subtle age-related declines in hippocampal gray matter, and no differences in parahippocampal, or anterior cingulate gyri are observed. In addition there are functional declines in the dopaminergic projections to the prefrontal cortex (Braver and Barch 2002), suggesting specific impairments to cognitive control, attention, and working memory (West 1996).

Global reductions in a number of cognitive abilities are observed across middle-aged and older adulthood. Perceptual speed, inductive reasoning, and spatial orientation are significantly impaired with age (Hedden and Gabrieli 2004). Verbal memory also declines but only later in life. However, autobiographical memory and emotional processing skills appear to remain intact. Within the memory domain, explicit memories show the greatest degradation with age, whereas implicit memory formation remains stable (Fleischman et al. 2004). While memory is generally observed to wane, it is important to assess whether sleep can benefit new memory formation with age.

1.6.2.1 Declarative Memory

A number of studies have shown declines in SDC with age (Harand et al. 2012; Pace-Schott and Spencer 2014). However, conflicting data, especially within the realm of declarative memory, make it difficult to assert a comprehensive argument about age-related changes in memory consolidation. While, compared to young adults, overall memory performance was reduced in middle-aged or older adults, SDC was still observed for declarative tasks – older individuals show improvements across sleep compared to wake (Aly and Moscovitch 2010; Wilson et al. 2012). Elderly women with greater sleep spindle density demonstrated enhanced declarative memory performance compared to those with reduced sleep spindle density (Seeck-Hirschner et al. 2012). In addition, sleep was shown to protect visuospatial declarative memories from interference in older adults, supporting a role of sleep in active memory stabilization (Sonni and Spencer 2015).

Comparatively, some research has shown no sleep benefit for declarative memory in aging populations. Backhaus and colleagues showed age-related reductions in SDC of declarative memory in middle-aged adults using a word-pair associates

task (2007). The impairments in memory were specifically associated with reduced SWS in the first half of the night. Importantly, when younger and middle-aged adults with similar SWS percentages were compared, there were no differences in memory consolidation. Visuospatial declarative memory consolidation was impaired in older adults; however, in this study, frontal SWA was associated with improved memory recall across all individuals, including both older and younger adults (Varga et al. 2016a). Older adults failed to demonstrate SDC of episodic declarative memories (Scullin 2013). Further, there was a strong correlation between SWS and episodic memory performance in younger adults, but no such relationship was observed in the older adults.

These results were paralleled in a more recent study of napping in older and younger adults (Baran et al. 2016). Older adults did not demonstrate a nap benefit on a declarative word-pair task, unlike the younger adults. Moreover, younger adult memory performance was positively correlated with the percentage of SWS and SWA in the nap and negatively associated with post-nap hippocampal activation during recall. This work suggests that even across a nap, systems-level restructuring of declarative information is occurring, leading to more stable long-term memories in younger adults. Older adult memory recall was not associated with either SWS in the nap or with reduced hippocampal activation. The authors concluded that sleep in older adults is less efficient at consolidating declarative memories.

To this end, recent work has examined whether enhancing SWS or oscillations in nREM sleep would recover SDC of declarative memories in older adults (Buckley and Schatzberg 2005). However, the results in this area of research are also conflicting. Westerberg and colleagues used transcranial current to artificially enhance slow oscillations during a nap in older adults in order to increase SWA (Westerberg et al. 2015). With the application of the current, SWA was increased, and declarative memory for word-pairs was improved. Contrarily, in another study, no memory improvements were observed across a nocturnal sleep bout when transcranial stimulation was applied during early SWS (Eggert et al. 2013).

1.6.2.2 Procedural Memory

The findings on SDC of procedural memories in older adults are more consistent. Performance on procedural tasks has been shown to not be improved by sleep in either middle-aged (Wilson et al. 2012) or older adults (Spencer et al. 2007; Brown et al. 2009; Wilson et al. 2012). Importantly, however, most of the procedural memory tasks used in older adults are sequence learning tasks (e.g., SRTT). Therefore, aging may specifically impair SDC of sequential information, not necessarily procedural skill more broadly.

In older rats, hippocampal replay of sequential information was significantly impaired during periods of rest (Gerrard et al. 2008). While the neuronal sequences were equivalently as active during rest in older rats as they were in younger rats, the temporal order of this activation was impaired. Further, the reduction in temporal order of replay was subsequently associated with impaired spatial memory. This

implicates sequence-specific information with impairments during aging. In support of this hypothesis, when older adults were tested on a non-sequential motor task, the mirror tracing task, SDC was observed (Mantua et al. 2016). More research is necessary to disentangle the relationship between sleep and procedural learning in older adults, with especial consideration for dissociating sequential and non-sequential information.

1.6.2.3 Emotional Memory

Lastly, few studies have examined how SDC of emotional information changes with age. Jones and colleagues showed that sleep protected both valence ratings and memory in older adults, but only for positive stimuli, not neutral or negative images (2016). In contrast, sleep in younger adults preserved valence ratings and memory for negative stimuli only.

This shift toward positivity may represent a bias toward well-being. Older adults have a positivity bias, focusing attention and on positive as opposed to neutral or negative stimuli (Carstensen and Mikels 2005; Mather and Carstensen 2005). With age, cognitive performance is significantly enhanced for positive emotional information (Carstensen and Mikels 2005), and even autobiographical memories are reported more positively with age than they were 14 years previously (Kennedy et al. 2004).

Age does not impair the activation of the emotional memory network during encoding of emotional stimuli (Kensinger and Schacter 2008). However, in comparison with younger adults, older adults had greater memory enhancement for positive stimuli during encoding; in addition, older adults showed greater activation in the mPFC and cingulate gyrus during presentation of the positive images. These authors similarly concluded that older adults might focus on more positive information, especially in reference to themselves.

1.6.3 Summary

With the progressive degeneration of the brain, especially in the mPFC, SDC in middle-aged and older adults becomes reduced. Reductions in SWS and SWA reflect subsequent changes in declarative memory consolidation. However, degradation of both the brain and sleep physiology may show strong inter-individual differences across aging, thereby influencing inter-individual differences in SDC. For example, when SWS in older adults parallels those in younger adults, SDC of declarative memory remains intact (Backhaus et al. 2007). Thus, improving SWS, and enhancing nREM sleep oscillations, may be a potential future therapeutic for age-related declines in memory.

Age-related changes in both procedural memory and emotional memory are unique. Changes in sequential neuronal firing may impair SDC of sequential

procedural tasks, but not procedural memory in general. Aging also changes the prioritization of emotional information for SDC. In young adults, negative emotional memories are prioritized for consolidation, whereas positive emotional memories are prioritized in older adults. Despite significant changes in sleep physiology, SDC of procedural and emotional information is not completely diminished.

1.7 Conclusions

Sleep is associated with memory consolidation across the life span. Changes in sleep and SDC reflect developmental changes within the brain. Prenatal brain development is reliant on sleep, and even in early infancy, sleep is associated with improved memory performance. At the other end of the life span, as the brain begins to progressively deteriorate, SDC is also diminished.

During early childhood development, nREM, and particularly SWS, plays the most prominent role in SDC. As synaptic connectivity proliferates with age, SWA subsequently increases. Memory consolidation in early childhood prioritizes explicit and hippocampal-dependent tasks. Following the massive synaptic pruning that occurs during puberty, SWS and SWA progressively decline. As a result, implicit tasks begin to show SDC in late adolescence and across adulthood. With the age-related degradation of frontal brain regions, SWS and SWA continue to decline significantly into older adulthood. As a result, SDC of declarative information becomes less efficient. In sum, the only times in which it is strongly debatable whether sleep benefits declarative memory consolidation are when the most dramatic reductions in SWS are observed: during adolescence and during older adulthood.

The functional role of other sleep stages on SDC is often debated. Primarily, SWS, or features of nREM sleep (slow oscillations, SWA, or sleep spindles), has been associated with all forms of memory consolidation in young children, including procedural and emotional memories. In adults, both REM and nREM2 (sleep spindles in nREM2 especially) have been connected with procedural memory consolidation. However, across the life span, evidence of SDC of procedural memory consolidation is the most inconsistent of the three memory classifications examined in this review. More recently, researchers are considering the relationship between nREM and REM sleep with respect to memory consolidation, rather than focus on one sleep stage in particular.

The evidence to support SDC in emotional memories is the most stable across the life span. With the exception of infancy, an age group for which no research in this area has yet been conducted, emotional memory consolidation is consistently demonstrated to benefit from sleep. Even into older age, prioritization of the consolidation of emotional memories is observed, although there is a positivity bias in consolidation as opposed to the negativity bias observed in other age groups. With respect to emotional memories, the most prominent SDC change across the life span is the attribution to particular sleep stages. In childhood and early adolescence, when the proportion of SWS is high across the night, SWS, SWA, and slow oscillations are

associated with emotional memory consolidation. In adulthood, with progressive declines of SWS occurring, both SWS and REM sleep are related to emotional processing.

The aims of this review were to address how sleep changes across the life span and how these changes influence memory consolidation. While much research has addressed this relationship in healthy young adults, the work in other age ranges is currently lacking. Given the dramatic changes in brain maturation and degradation across the life span, as well as the remarkable changes in sleep architecture and physiology, there is immense need for future research on SDC in infancy, early childhood, adolescence, middle-aged, and older adulthood.

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Chapter 2
Sleep Deprivation, Cognitive Functions, and Countermeasures

Usha Panjwani, Meetu Wadhwa, Koushik Ray, and Krishna Kishore

Abstract Sleep is necessary for the execution of cognitive functions. Sleep disturbance causes cognitive impairment in humans as well as rodents. Sleep is essential for neurogenesis, synaptic plasticity, and hippocampus-based memory consolidation. This process is impaired by sleep deprivation and may involve multiple pathways. Hippocampus is an essential player in the brain, which is involved in the execution of various cognitive functions and maintains neurogenesis and synaptic processes. At the same time, it is also more vulnerable to stress. Caffeine and modafinil are recognized psychostimulants, known to improve sleep deprivation-induced cognitive function decline in humans as well as animals. Caffeine and modafinil are well-evaluated countermeasures against sleep deprivation-induced alterations in the neuronal cell proliferation and synaptic plasticity mechanism. The article describes the sleep deprivation-induced deficit in cognitive function, its molecular mechanism, and the effect of psychostimulant drugs, caffeine, and modafinil.

Keywords Sleep deprivation · Cognition · Caffeine · Modafinil · Neurogenesis · Synaptic plasticity

Abbreviations

ABP	Arterial blood pressure
ACTH	Adrenocorticotropic hormone
BDNF	Brain-derived neurotrophic factor
BL	Baseline
BP	Blood pressure
CA	Cornu Ammonis
Caf	Caffeine

U. Panjwani (✉) · M. Wadhwa · K. Ray · K. Kishore
Neurophysiology Division, Defence Institute of Physiology & Allied Sciences (DIPAS), Defence Research and Development Organization (DRDO), Delhi, India

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CNV	Contingent negative variation
CRH	Corticotropin-releasing hormone
DCX	Doublecortin
DG	Dentate gyrus
EC	Entorhinal cortex
ERP	Event-related potential
HC	Hippocampus
HR	Heart rate
HRV	Heart rate variability
LTD	Long-term depression
LTP	Long-term potentiation
Mod	Modafinil
MWM	Morris water maze
NORT	Novel object recognition test
NREM	Non-rapid eye movement
REM	Rapid eye movement
SD	Sleep deprivation
SGZ	Subgranular zone
SVZ	Subventricular zone
WCST	Wisconsin Card Sorting Test

2.1 Sleep Deprivation: A Phenomenon of Modern Lifestyle

Sleep loss is now recognized as a major problem inherent in modern society. The major factors responsible for sleep disturbance are the competitive lifestyle with professional demands. In humans, the sleep of less than 8 h, and in rodents, any time duration the animal is kept awake forcefully, is termed as sleep deprivation. Sleep deprivation can be either of shorter duration of time (acute) or for long periods (chronic). Acute sleep deprivation leads to poor scores on behavioral tasks involving attention, vigilance, learning, and memory. Reasoning ability, innovative thinking, and decision-making are also impaired. After acute sleep deprivation, the presence of fatigue and need for sleep are persistent. The presence of tremor, discomfort, and increased tonus may also be observed. Task performance may be hampered with a decreased concentration. The sleep-deprived individual becomes irritable and aggressive. Prolonged micro-episodes, perception disorder, illusions, and hallucinations may be experienced. As the duration of sleep deprivation increases, the symptoms become more severe including reasoning disability, disorientation, visual problems, and delusions. Distrust, depersonalization, and attempts to murder-like symptoms are characteristics of chronic sleep loss. Thus, both acute and chronic sleep deprivation have adverse effects on the brain and cognitive functions, but the consequences of chronic sleep loss or disturbance are more severe than acute sleep deprivation. Sometimes sleep loss lasting for several days leads to a compromised day-to-day functioning in common mental tasks (Siegel 2005).

2.1.1 Consequences of Sleep Deprivation

Most of the physiological functions of the body are altered during sleep deprivation, such as autonomic, temperature regulation, hormonal secretion, and immune and cognitive functions. Cardiovascular perturbations are dominant during sleep stages, non-rapid eye movement (NREM) and rapid eye movement (REM). These changes result because of the autonomic both sympathetic and parasympathetic nervous system fluctuations. Various experimental procedures have been adopted to investigate sleep deprivation-mediated consequences in healthy subjects. After acute sleep loss, arterial blood pressure (ABP), heart rate (HR), and blood pressure (BP) tend to rise. Heart rate variability (HRV) analysis shows an enhanced sympathetic activity (increased low frequency component, increased low frequency/high frequency component ratio, reduced vagal control). In a study, during partial sleep deprivation, there was a decrease in vasodilatation without any alteration in autonomic profile, whereas HRV was reduced with significant variations in autonomic parameters after chronic sleep deprivation in healthy subjects (Tobaldini et al. 2016).

Sleep loss affects the immune system with an upregulation in the production and release of pro-inflammatory cytokines. Infections may develop with sleep deprivation due to immunological suppression. During acute sleep deprivation, there is an increase in the concentration of IgG, IgA, and IgM and a reduction in helper T-cell count and natural killer cells. Sleep loss induces an increase in the metabolic rate, food intake, appetite, and hunger and decreases the concentration of leptin with a decrease in body mass. Sleep deprivation influences the hormonal balance, the level of thyroid hormones (thyroxine and triiodothyronine), and corticotropin-releasing hormone (CRH) level in the hypothalamus. Plasma aldosterone and renin concentration decrease, while adrenocorticotropic hormone (ACTH), corticosteroids, and noradrenaline increase, whereas growth hormone level remains unaltered (Orzel-Gryglewska 2010).

Sleep disturbance has been found to be responsible for structural as well as functional changes in the brain. During chronic sleep deprivation, the average rate of brain metabolism is lowered, disrupting the functional capacity of the brain as shown by behavioral changes such as reduced alertness, performance, precision, and cognitive functions. Functional magnetic resonance imaging shows that after sleep deprivation, some brain areas become more active while other brain areas show reduced activity. Studies on humans have shown an impairment in the acquisition and encoding phase of memory following acute sleep loss (Yoo et al. 2007).

Event-related potential (ERP) provides information about the cognitive process including attention, vigilance, concentration, and working memory. Sleep deprivation induces an alteration in ERP morphology. Sleep deprivation reduced the onset and amplitude of P300 (a response as deflection at 300 ms) using the oddball paradigm. Contingent negative variation (CNV) is a measure of readiness to receive a stimulus, also dubbed as “expectancy wave.” During sleep deprivation (24 h) in humans, the sleepiness score, latency of P300 ERP, and reaction time were increased which indicated a reduced information-processing ability. Various parameters such

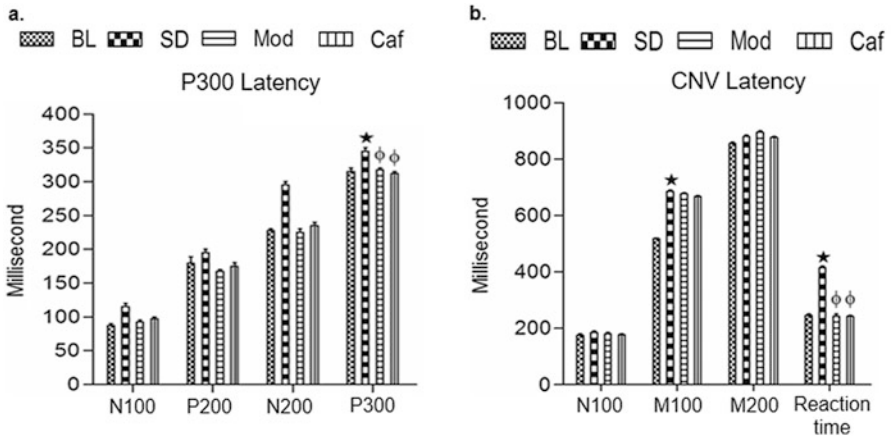

Fig. 2.1 Effect of caffeine and modafinil on event-related potential components during sleep deprivation. Parameters: (**a**) P300, (**b**) CNV Latency. $^{*}p < 0.05$ as compared to baseline, $^{\Phi}p < 0.05$ when compared to sleep deprivation. One-way ANOVA with Bonferroni post hoc test was used for the statistical analysis

as N100 latency (processing of stimulus), P300 latency, CNV latency, and M100 latency were delayed with no significant alteration in N200 latency (stimulus detection) and CNV amplitude (Fig. 2.1) (Ray et al. 2012).

2.1.2 Therapeutic Strategies for Optimization of Cognitive Functions During Sleep Deprivation

Amelioration of cognitive dysfunction following sleep deprivation is an inescapable necessity. There are pharmacological as well as non-pharmacological strategies available against the sleep deprivation-induced dysfunction. The pharmacological treatment includes the readily available stimulants like caffeine, energy drinks, and wake-promoting agent like modafinil. These are beneficial in the improvement of cognitive performance during sleep deprivation (De Valck and Cluydts 2001).

Caffeine acts as a nonselective adenosine receptor antagonist. It is widely used as a stimulant and cognitive enhancer and also consumed in food, beverages, etc. Caffeine has a neuroprotective role against stress-mediated cognitive impairment. It improves the alertness, vigilance, and concentration during sleep deprivation (Bonnet et al. 2005). Modafinil is a wake-promoting drug; its wake-promoting property is due to the competitive binding to dopamine transporter and adrenergic signaling. It is used to treat patients of sleep-related disorders such as narcolepsy, shift work, and sleep apnea; however, the mode of action appears to be multifactorial, and exact mechanism involved in its wake-promoting property is not well understood.

In a study of prolonged sleep deprivation, it was reported that caffeine and modafinil decreased errors and improved scores of Wisconsin Card Sorting Test (WCST) and Stroop test (Wesensten et al. 2004). Modafinil also reduced the latencies of P300 and CNV wave forms during sleep deprivation. Caffeine and modafinil treatment also maintained the cognitive performance as shown by the reduced P300 peak latency, M100 latency, and CNV reaction time following one night of sleep deprivation. However, no major changes in the latency of N100, P100, N200 ERP, and M200 latency during one night sleep deprivation and caffeine/modafinil treatment were found (Fig. 2.1a, b).

The beneficial effect of modafinil may be due to the increased release of histamine, dopamine, and serotonin via inhibiting their transporters (Ray et al. 2012). Alternative non-pharmacologic strategies can also attenuate the negative effects of sleep deprivation. Napping was found to be effective in improving the cognitive functions following 24 h of sleep deprivation as shown by reduced sleepiness score, P300 peak latency, CNV M100 peak latency, and CNV reaction time (Panjwani et al. 2010). Meditation practice for 2 months was also reported to be effective against cognitive dysfunction during sleep deprivation (Chatterjee et al. 2012).

2.2 Sleep Deprivation Studies in Rodents

Rat is the most commonly used animal model for sleep deprivation or restriction studies in order to examine the consequences of sleep deprivation at behavioral, biochemical, molecular, and cellular level. Following chronic sleep deprivation, rats present with sleep deprivation syndrome with changes in food intake, body weight, and thermoregulation, leading to death in case of prolonged sleep deprivation (Rechtschaffen 1998).

2.2.1 Animal Models of Sleep Deprivation

There are several methods that have been used for sleep deprivation in rodents such as flowerpot method (used for selective REM sleep deprivation), forced locomotion, gentle handling, or mild tactile stimulation sometimes including novel material, novel place, etc. Each method has its own advantages and disadvantages. For example, in the forced locomotion method, the effects of sleep deprivation are sometimes reversed or masked because of motor activity, which will give an exercise component, itself a confounding variable. On the other hand, gentle handling technique is laborious needing a constant monitoring as well as a stress for the animal which is suitable for acute but not chronic sleep deprivation studies (Sahu et al. 2013).

2.2.2 *Novel Automated Sleep Deprivation Model*

We developed a novel software-operated method of sleep deprivation that can be used for long-duration sleep deprivation studies (few days) with no need for constant monitoring and 70–90% wakefulness. Using this novel automated method, rats underwent sleep deprivation based on a behavioral scale (Fig. 2.2). Sleep deprivation apparatus includes a tracking software, infrared camera, interface, amplifier, and shaking pads (ANY-maze, Stoelting, USA). The animals are placed in acrylic cages (transparent, open top) individually, and the overhead infrared camera monitors the animal constantly. Data analysis is performed by the ANY-maze software which records freezing and immobility parameters. The interface of ANY-maze is driven by the software, which switches on the amplifier and in turn gives a command to the shaking pads positioned below the cages to give vibration to the immobile animal. Cages are set in side by side with holes on the cage walls to avoid isolation (Sahu et al. 2013; Wadhwa et al. 2015).

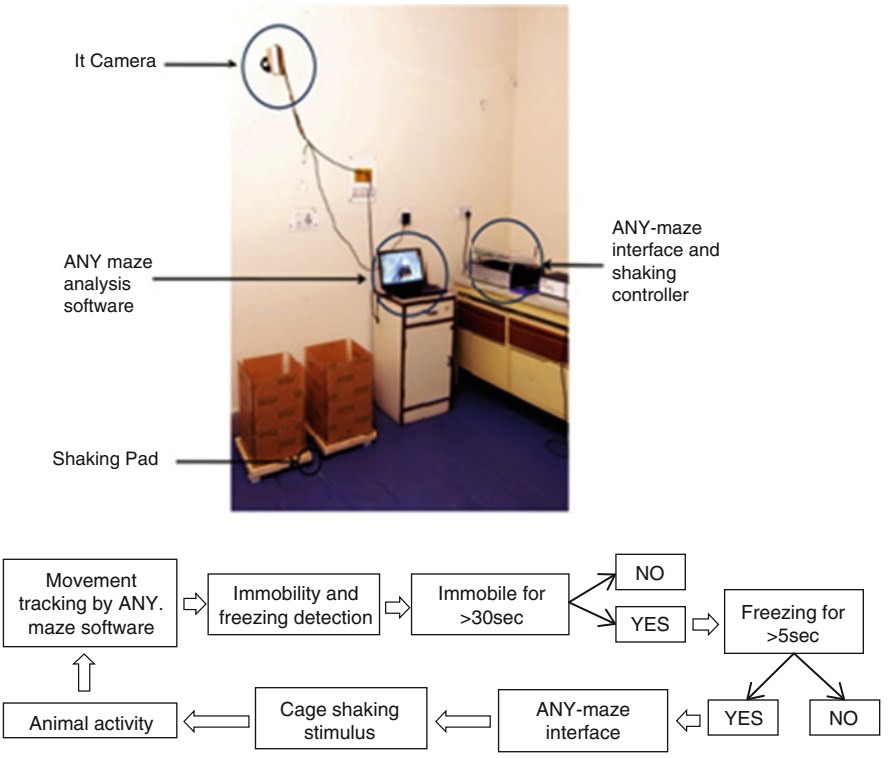

Fig. 2.2 Sleep deprivation setup

2.3 Changes in Learning and Memory During Sleep Deprivation and Therapeutic (Caffeine/Modafinil) Interventions

Sleep loss has been found to impair cognitive performance in humans as well as rodents (Tripathi and Jha 2016). It has been reported that sleep loss produces spatial memory impairment in the Morris water maze (MWM) tasks in rodents (Rauchs et al. 2008). The study in our laboratory revealed that spatial memory performance in MWM test decreased gradually during 48 h sleep deprivation and caffeine/modafinil treatment improved spatial reference memory following sleep deprivation exposure as shown by the track plot (Fig. 2.3a) and test parameters such as path length and path length to reach the target platform (Unpublished Fig. 2.3b, c). There are reports of improved vigilance, psychomotor activities, and fatigue following caffeine and modafinil treatment during sleep deprivation. After sleep deprivation, working memory task is diminished in mice, and modafinil treatment is reported to restore the spatial working memory performance (Killgore et al. 2008; Pierard et al. 2007). Evidence suggests the importance of sleep in the proper encoding, storage, and retrieval of memory during the training phase; besides, sleep also plays an important role in the acquisition of information (Yoo et al. 2007).

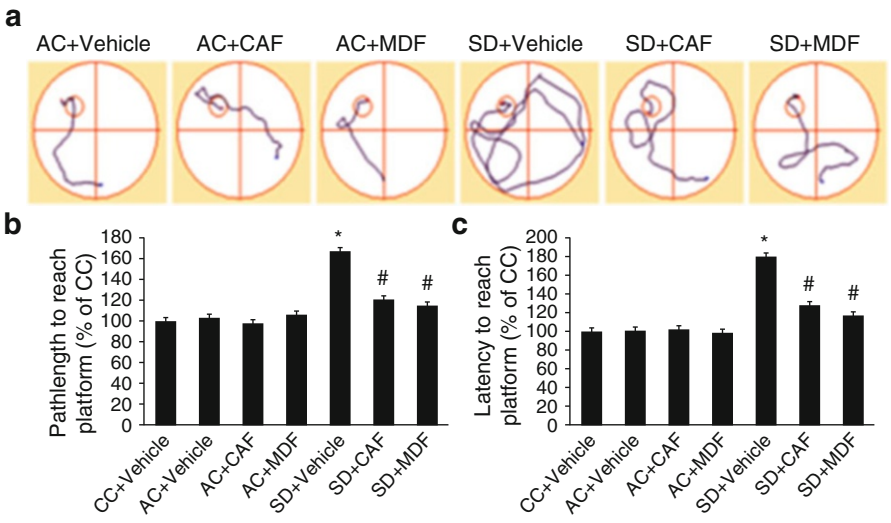

Fig. 2.3 Effect of caffeine and modafinil on sleep deprivation-induced spatial memory impairment. (**a**) Track plot of memory performance of rats. Test parameters: (**b**) path length, (**c**) latency to reach platform. $^{*}p < 0.05$ as compared to control treated with vehicle, $^{\#}p < 0.05$ as compared to sleep deprived treated with vehicle. One-way ANOVA with Bonferroni post hoc test was used for the statistical evaluation

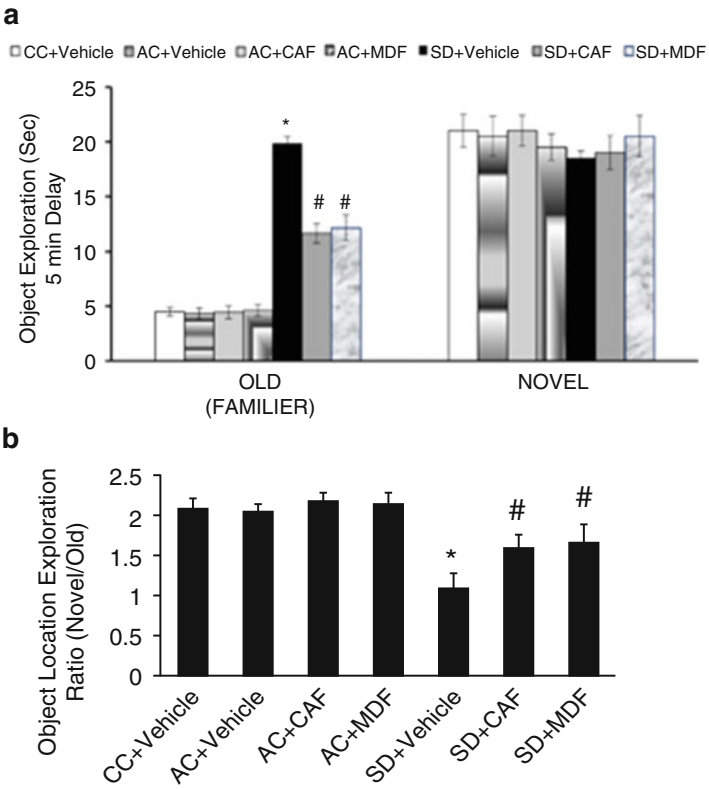

Fig. 2.4 Effect of caffeine and modafinil on sleep deprivation-induced recognition memory impairment. Test parameters: (**a**) object exploration time, (**b**) object location exploration ratio. $^{*}p < 0.05$ as compared to control treated with vehicle, $^{\#}p < 0.05$ as compared to sleep deprived treated with vehicle. One-way ANOVA with Tukey-Kramer multiple comparison test was used for statistical evaluation

Recognition memory is the ability to distinguish novel and familiar stimuli. To study the recognition memory, novel object recognition test (NORT) is widely used. Sleep improves the recognition memory, and any change in sleep impairs the exploration, discrimination, and recognition memory. Improvement in the recognition memory has been reported following acute caffeine/modafinil administration. After 48 h of sleep deprivation, novel object and location recognition memory (5 min delay) in NORT were impaired, and caffeine/modafinil administration improved recognition memory performance during the 48 of h sleep deprivation period (Fig. 2.4a, b) (Wadhwa et al. 2015).

2.4 Mechanisms of Sleep Deprivation-Induced Cognitive Decline

Hippocampus is known as a storage house of memories, which is composed of dentate gyrus (DG), subfields of Cornu Ammonis (CA), and entorhinal cortex (EC). Experimental studies of synaptic plasticity in the hippocampus are designed based on the trisynaptic excitatory pathways between DG, CA1, and EC regions (Scoville and Milner 1957). Several explanations are proposed to explain the impairment of cognitive performance during sleep loss; however, the exact mechanism may involve multiple pathways.

2.4.1 Role of Neuronal Cell Proliferation in Sleep Deprivation-Mediated Changes in the Learning and Memory Performance

Hippocampus is an important site of adult neurogenesis mainly involving sub-ventricular zone (SVZ) and subgranular zone (SGZ) of the DG region. Adult neuronal cells are generated, proliferate, and finally integrate into the neuronal network loop in the hippocampus. Dorsal and ventral hippocampal regions have a role in regulation of neurogenesis and cognition (Deng et al. 2010). Neurogenesis consists of stages such as proliferation, differentiation, survival, and integration, which are known to be modulated by neurotrophins, neurotransmitters, cytokines and drugs, etc. via receptor signaling pathways and epigenetic and transcription factors. There is a strong association between adult neurogenesis and learning/memory process in the hippocampus. Neurogenesis in adult mice correlates positively with learning ability. This is proven by direct evidence: depletion of adult-generated neurons leads to impairment of specific learning tasks like associative learning and fear conditioning. In another study, genetic ablation of rat adult-born neuronal cells decreased the neuronal cell count in DG region, which led to hippocampus-based behavioral abnormalities. On the other hand, hippocampal neurogenesis facilitates synaptic plasticity in the hippocampus (Kitamura et al. 2009).

Growing evidence supports the association between sleep and adult neurogenesis. Recently, sleep and adult neurogenesis have received widespread attention. Sleep favors the neurogenesis process, and any impairment in sleep function produces a decrement in the adult neuronal cell proliferation process in the hippocampus. Acute sleep deprivation did not reduce neurogenesis in sub granular zone of hippocampus; however more than 24 h of total sleep deprivation decreases neurogenesis in the hippocampus (Roman et al. 2005). REM sleep deprivation decreases the cell counts

of proliferating neurons in DG region, whereas immature neuronal cells' number reduces after both REM and NREM sleep deprivation. There are reports of the suppression in the adult neuronal proliferating cell count following sleep disruption of varying durations. A previous study reported the decrement of proliferative neuronal cells as shown by BrdU and doublecortin (DCX; proliferative, intermediate, and postmitotic stage) positive cell counts in the DG region of the hippocampus following 48 h of sleep deprivation. However, no change in the maturational marker of neurogenesis (NeuN) was seen during 48 h of sleep deprivation (Sahu et al. 2013). An association between sleep loss and reduced neurogenesis has also been validated by other studies employing various procedures such as platform method, treadmill, and disk-over-water (Roman et al. 2005).

There are reports about the neuroprotective role of caffeine or modafinil on neuronal cell proliferation process. There is a dose-dependent effect of caffeine on the neurogenesis: low-dose treatment for a shorter period had no effects on adult neuronal cell proliferation, and acute supraphysiological dosage promoted neurogenesis, while very higher dosage repeatedly used decreased neurogenesis and impaired cognition. Treatment of caffeine or modafinil attenuated the reduction of BrdU-positive cell count during 48 h of sleep deprivation (Fig. 2.5a). During 48 h of sleep deprivation, the decrement in the proliferative DCX-positive cell count was found to be attenuated by only caffeine treatment, while the numbers of intermediate-stage DCX-positive cells were improved by only modafinil treatment. On the other hand, postmitotic stage DCX-positive cell count was improved by both caffeine and modafinil during sleep deprivation (Fig. 2.5b) (Sahu et al. 2013). Besides sleep deprivation, caffeine or modafinil treatment also plays a significant role in the improvement of neurogenesis in other stress conditions (Kochman et al. 2009).

Recently, brain-derived neurotrophic factor (BDNF) has emerged as an important regulator of sleep as shown by studies, which report onset of sleep via cortical BDNF expression. BDNF increases spontaneous sleep in rodents (Bachmann et al. 2012). Sleep loss decreases the BDNF expression in the hippocampus, which is improved by caffeine administration. BDNF enhances the hippocampal functions by increasing the adult neuronal cell proliferation and other processes related to the neurogenesis (Alhaider et al. 2011). Gene silencing of hippocampal BDNF by different means produces a negative impact on neurogenesis (Taliaz et al. 2010). The beneficial effects of caffeine in maintaining physiological BDNF level and cognitive functions under stressful conditions such as obesity or aging are reported (Alzoubi et al. 2013). We reported that 48 h sleep deprivation significantly decreased the expression of BDNF in the DG region of the hippocampus, which was found to be improved by caffeine/modafinil treatment (Fig. 2.5c). Caffeine/modafinil administration improved the adult neuronal cell proliferation and differentiation by enhancing the level of BDNF protein in the hippocampus during sleep deprivation. Previous literature also supports the role of BDNF expression in adult newborn

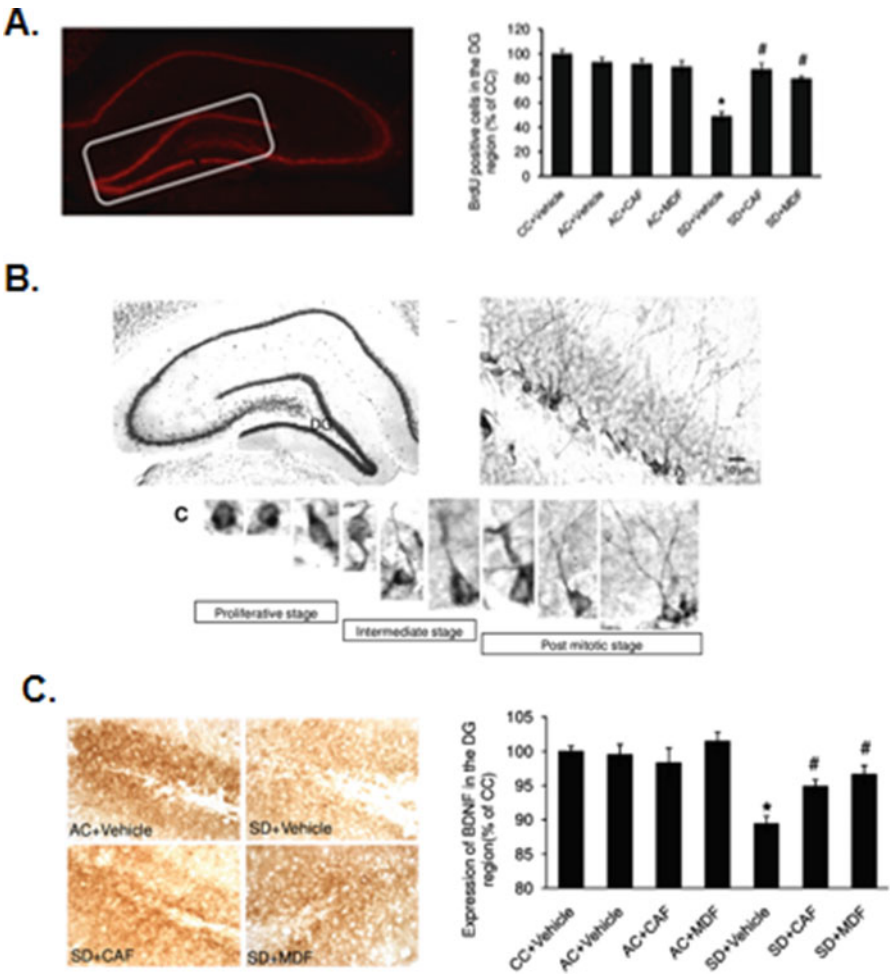

Fig. 2.5 Effect of caffeine and modafinil on changes in proliferation, differentiation, and growth factor proteins during sleep deprivation. Changes in: (**a**) representation of DG region of the hippocampus and BrdU cell count in DG region, (**b**) identification of different stages of DCX-positive cells in DG region of the hippocampus, and (**c**) representative images of BDNF expression in DG region of the hippocampus and changes in the relative mean pixel intensity of BDNF in DG region of the hippocampus. $^{*}p < 0.05$ as compared to control treated with vehicle, $^{\#}p < 0.05$ as compared to sleep deprived treated with vehicle. One-way ANOVA with Tukey-Kramer multiple comparison test was used for statistical evaluation

neurons (Sahu et al. 2013). Hence, caffeine and modafinil treatment during sleep deprivation produce neuroprotective effects by the attenuation of reduced adult neuronal cell proliferation via BDNF expression.

2.4.2 *Role of Synaptic Plasticity in Sleep Deprivation-Induced Learning and Memory Impairment*

In addition to neurogenesis, hippocampus also maintains synaptic plasticity, a dynamic process by which the strength of the connection between neurons continuously changes over time to enable the brain to learn and store memories. The synapse, a highly specialized structure that allows communication between the neurons, is composed of three main elements: the presynaptic terminal, the synaptic cleft, and the postsynaptic membrane. Long-term potentiation (LTP) in the hippocampus is the basis for formation of new learning and memory (Malenka and Bear 2004). BDNF enhances the synaptic transmission and influences synaptic plasticity by the activation of CaMKII protein in the hippocampus. BDNF is essential for the induction and maintenance of LTP in the hippocampus. It also plays a role in synaptic potentiation. There is an increase in the mRNA level of BDNF in the hippocampus during spatial learning (Kesslak et al. 1998). Everyday functions, such as remembering the events of a particular day or learning to navigate around different places, depend on this process of synaptic communication. Morris water maze experiments have shown that rats lose the ability to navigate a known route when synaptic plasticity is blocked (Morris 1989).

Synaptic modulation has a role in the regulation of sleep-wakefulness as documented by molecular studies. Sleep, particularly NREM stage, maintains the restoration process of cells by the transcriptional and translational control in the synthesis and transport mechanisms of macromolecules. NREM sleep loss induces synaptic down-scaling, morphological alteration in synapses (shrinkage), leading to reduce synaptic efficacy. Transcriptional reactivation of immediate early genes (Arc, BDNF, and zif268) happens during REM sleep, while wakefulness is associated with memory consolidation and neuronal activity replay, which have been proposed to be related with sleep (NREM) events such as wave ripples and sleep spindles in the hippocampus. Modulation in the gene expression (REM sleep) and synaptic replay (NREM sleep) favors the synaptic consolidation (Gronli et al. 2013). There are limited studies that examine the effect of sleep deprivation on long-term depression (LTD). It had been found that sleep deprivation for 12 h induced LTD in CA1 region of rat hippocampus (Tadavarty et al. 2009). Sleep loss accelerates the synaptic depression and inhibits synaptic potentiation in the hippocampus. There are some studies which have evaluated the effects of sleep disruption on synaptic plasticity; however, only a limited number of studies investigate the molecular signaling

mechanisms involved in the modulation of synaptic dynamics during sleep deprivation. Sleep loss had been reported to disturb the synaptic homeostasis as shown by the reduction in the immune reactivity and density of synaptic proteins in different regions of the hippocampus (Wadhwa et al. 2015).

Under stressful conditions including sleep loss, administration of caffeine decreases changes in the synaptic plasticity. Long-term treatment of caffeine ameliorated fold changes in phosphorylated CaMKII and altered BDNF expression during early phase of LTP during sleep deprivation (Alhaider et al. 2010). There are limited studies on the effects of modafinil on molecular correlates of synaptic plasticity. Modafinil prevents REM sleep deprivation-induced brain function impairment. Modafinil was reported to upregulate synapsin-1 expression in the dorsal hippocampal CA3 region, along with population spike amplification and augmentation in postsynaptic potentials interrelated to theta rhythm (Tsanov et al. 2010).

The vulnerability of dorsal hippocampus to sleep loss is documented by behavioral changes. Sleep is directly linked to learning, memory, and neural plasticity. During wakefulness, the exposure of surroundings strengthens the synaptic connections in the brain and enhances the learning process. This results in increased demands of the cells for energy and micronutrients, which reduces synaptic strength. During sleep, spontaneous activity stabilizes the synaptic strength and reestablishes homeostasis. The downregulation of synaptic proteins during sleep deprivation supports the beneficial role of sleep in the memory processing (Tononi and Cirelli 2014). The presynaptic regulatory proteins' synaptophysin and synapsin expression in the hippocampus was reduced after sleep deprivation and improved by caffeine/modafinil treatment. Postsynaptic density protein 95 expression in the hippocampus was decreased after sleep deprivation. Modafinil treatment during sleep deprivation increased the expression of PSD 95 in the hippocampus during sleep deprivation. The attenuation of the reduced levels of synaptic plasticity molecules following caffeine/modafinil treatment during sleep deprivation may be involved in the enhancement of cognitive performance (Fig. 2.6a–d) (Wadhwa et al. 2015).

2.5 Concluding Remarks

Sleep deprivation compromises cognitive functions including attention, concentration, learning, and memory in humans as well as animals. Sleep loss diminishes the neuronal cell proliferation and expression of synaptic plasticity molecules in the adult rat hippocampus. The cognitive changes during sleep-deprived conditions may be linked to the changes in the neurogenesis and synaptic plasticity. Psychostimulant drugs, caffeine, and modafinil improve the adult neuronal cell proliferation, preserve synaptic plasticity, and facilitate cognitive performance during sleep deprivation.

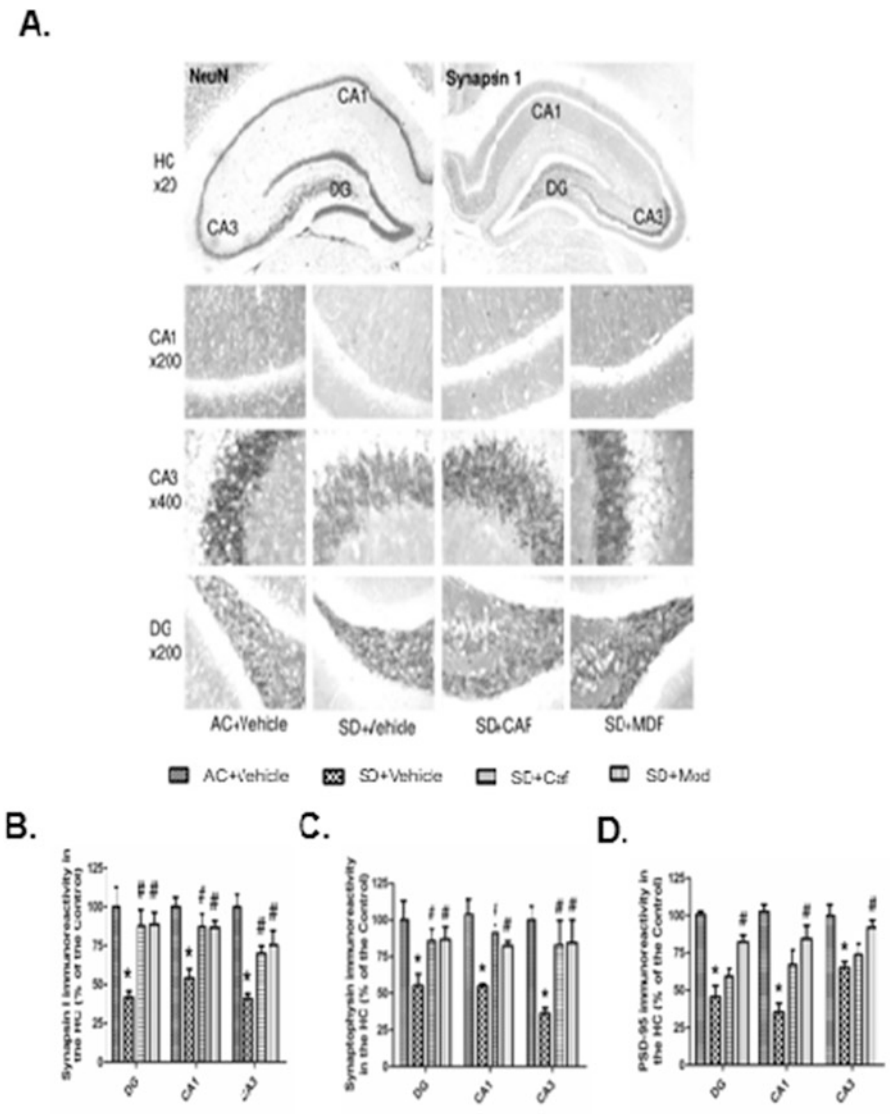

Fig. 2.6 Effect of caffeine and modafinil on sleep deprivation-induced changes in synaptic proteins' expression in the hippocampus. (**a**) Representative image showing synapsin-1 expression in DG, CA1, and CA3 region of the hippocampus. Changes in the relative mean pixel intensity of (**b**) synapsin-1, (**c**) synaptophysin, and (**d**) PSD-95 proteins in DG, CA1, and CA3 region of the hippocampus. $^{*}p < 0.05$ as compared to control treated with vehicle, $^{\#}p < 0.05$ as compared to sleep deprived treated with vehicle. One-way ANOVA with Tukey-Kramer multiple comparison test was used for statistical evaluation

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Chapter 3
Sleep Loss and Neuronal Stress

Nirinjini Naidoo

Abstract Sleep loss and insufficient sleep are increasingly prevalent in most societies these days. Besides the well-known effects of sleep loss such as motor vehicle and workplace accidents, studies have shown a myriad of physiological consequences including increased risk for type 2 diabetes, obesity, and cardiovascular disease. Sleep loss is known to impair cognition and affect learning and memory. More recent studies have demonstrated a link between sleep loss, neuronal stress, injury, and degeneration. Both acute and chronic sleep loss as well as sleep fragmentation have been shown to impact neurons at a molecular level and lead to injury and sometimes death. Mechanisms and pathways involved will be discussed in this chapter.

Keywords Sleep · Cellular stress · Protein homeostasis · Neuronal injury

3.1 Introduction

We have increasingly become a 24/7 society with more of us losing or sacrificing sleep each night to keep up with the demands of daily life. Sleep deprivation may occur because of acute sleep loss for certain period or having insufficient sleep for several days. Chronic insufficient sleep or sleep loss is defined as having less than 6 h sleep per 24 h (Liu et al. 2013). Sleep loss is common in the American population where insufficient sleep is prevalent among 30% of employed adults representing over 40 million individuals (MMWR 2012). Some groups, such as medical professionals (physicians, nurses), investment banking analysts (http://news.efinancialcareers.com/us-en/196881/10-worst-banks-working-hours/), (abc news http://abcnews.go.com/Business/bank-america-investment-banking-analysts-jumping-joy-firms/story; http://www.businessinsider.com/investment-banking-

N. Naidoo (✉)
Center for Sleep and Circadian Neurobiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA
e-mail: naidoo@mail.med.upenn.edu

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internship-nightmare-2013-8), and college students, are suffering from sleep loss mainly because of their schedules. A survey conducted among college students showed that approximately 25% of students obtain less than 6.5 h of sleep and about 70% sleep less than 8 h per night (Lund et al. 2010). This prevalence of sleep loss has resulted in the release of two IOM (Institute of Medicine) reports addressing the problem – Sleep Disorders and Sleep Deprivation: An Unmet Public Health Problem and Optimizing Graduate Medical Trainee (Resident) Hours and Work Schedule to Improve Patient Safety (Colten et al. 2006; Ulmer et al. 2009). Chronic sleep loss among adolescents is not exclusive to the USA; in South Korea, short sleep is so prevalent that one large study has reported the mean sleep time to be approximately 4.9 h/night (Yang et al. 2005). Sleep loss has a number of consequences. Sleep deprivation or restricted sleep causes wake-state instability (Chee et al. 2006) where maintaining stable wakefulness is compromised with individuals drifting in and out of sleep. Sleep loss induces performance deficit and impairs executive attention, working memory, and several other aspects of cognitive function (Dinges 1992; Goel et al. 2009). It is estimated that almost 20% of motor vehicle crashes are attributed to driver sleepiness independent of alcohol consumption (Connor et al. 2002). Sleep loss also has detrimental effects on metabolic and cardiovascular functions. Epidemiological studies have found a close link between sleep disturbances and increased risk of obesity, type 2 diabetes, and cardiovascular disease (Grandner 2014; Grandner et al. 2014; Knutson 2012; Knutson et al. 2010). People reporting short sleep durations (typically less than 6 h/night) have been shown to display increased prevalence of obesity, hypertension, type 2 diabetes, cardiovascular disease, and stroke (Ayas et al. 2003; Chen et al. 2008; Elliott et al. 2014; Qureshi et al. 1997; Spiegel et al. 2005). While metabolic and cardiovascular effects of chronic sleep loss have been demonstrated (Kaneita et al. 2008; Lusardi et al. 1999; Spaeth et al. 2013), much less is known of long-term neurobehavioral and molecular consequences of inadequate sleep. This chapter will focus on known molecular changes that occur with sleep loss with special emphasis on cellular stress and antioxidant mechanisms. Pathways activated by both acute and chronic sleep loss and the subsequent effects on neuronal injury and survival will be described.

3.2 Molecular Correlates of Sleep Loss

In order to understand the molecular and cellular consequences of sleep loss, many groups have used animal models and sleep disruption/deprivation protocols to discern some of the mechanisms involved. These sleep loss inducing protocols have historically included gentle handling, platform over water technique, and forced locomotion. Continuous sleep deprivation of rats using the disc over water method has been shown to be lethal (Everson et al. 1989). More recently,

optogenetics and chemogenetic techniques have been used to stimulate wake-active neurons to produce prolonged waking and sleep fragmentation and have resulted in a greater understanding of the effects of sleep loss at both the circuit and molecular level.

Several microarray and transcriptomic and to a lesser extent proteomic studies over the past few years have begun to elucidate some of the molecular correlates of sleep loss. A downregulation of macromolecular synthetic processes with acute sleep loss has been described (Mackiewicz et al. 2007) suggesting that sleep is a period of biosynthesis and restoration. Concomitantly, the upregulation of immediate early genes and molecules involved in energy regulation and metabolism and an adaptive cellular stress response to acute sleep loss is consistently observed among all studies (for comprehensive list of transcripts, see review by Elliott et al. (2014)). Immediate early transcripts/genes encoding proteins involved in synaptic plasticity, i.e., Bdnf, Arc, Homer 1a, and NGF1-A (Cirelli et al. 2004; Huber et al. 2007), have been shown to be prominently upregulated with short periods of sleep loss. In addition, the upregulation of the molecular chaperone BiP (immunoglobulin-binding protein) which is a sentinel marker of a cytoprotective cellular stress response, the unfolded protein response (UPR), is conserved across all species studied (Naidoo 2009). Acute sleep deprivation has been shown to increase BiP/GRP78 expression in the brains of mice (Mackiewicz et al. 2007; Maret et al. 2007; Naidoo et al. 2005), rats (Cirelli et al. 2004; Terao et al. 2006), birds (Jones et al. 2008), and fruit flies (Naidoo et al. 2007; Shaw et al. 2000; Williams et al. 2007). Upregulation of many key components of the UPR signaling pathways (described below) during sleep loss have also been described by several groups (Fig. 3.1 and for details, see Naidoo 2009). A brief overview of the UPR describing the initial cytoprotective response of the UPR and the later pro-apoptotic signaling pathway as a consequence of sleep loss are summarized below. Findings of sleep deprivation and intermittent hypoxia studies demonstrate a role for the UPR, and antioxidant pathways in sleep are described. Understanding how sleep loss alters several pathways and the precise mechanisms underlying it will help in developing therapies to protect the brain from neuronal stress incurred during sleep loss and in sleep disorders including those associated with aging.

3.3 The UPR, an Adaptive Mechanism That Reduces Cellular Stress, Is Induced by Acute Sleep Loss

The unfolded protein response (UPR) is a protein homeostatic pathway that is triggered when endoplasmic reticulum (ER) stress is induced. In the ER, all secretory and integral membrane proteins are posttranslationally modified and folded in ATP-dependent chaperone-mediated processes (Walter and Ron 2011). Steroid,

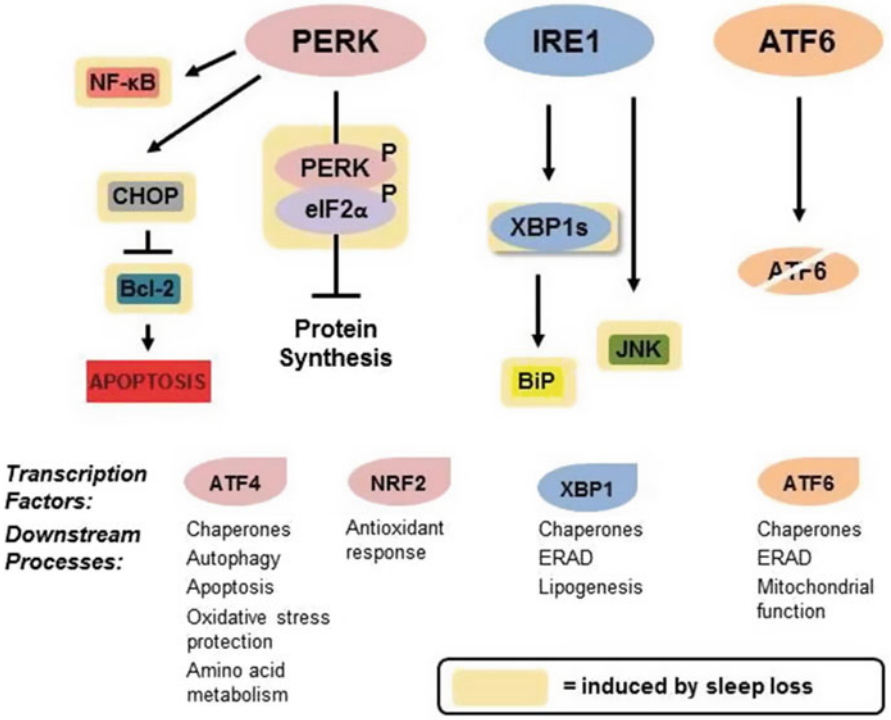

Fig. 3.1 A simplified schematic of the UPR showing transcription factors and downstream signaling pathways activated by ER stress. Transcripts and proteins induced by sleep loss are highlighted

cholesterol, and lipid biosynthesis also take place in the ER. It is one of the major signal-transducing cell organelles that release calcium in response to environmental cues (Kaufman 2002). Since the endoplasmic reticulum has an extensive membranous network that spreads throughout the cytoplasm flanking the nuclear envelope, so it plays an important role in sensing and transmitting signals that originate in any cellular sub-compartment. Thus perturbing ER homeostasis disrupts protein folding, and as a result, there would be accumulation of more unfolded proteins and protein aggregates, which are deleterious to cell survival. The UPR conveys signals from the ER to the nucleus and cytosol through the activation of three transducers of the ER stress signal: PERK (PKR like ER kinase), ATF6 (activating transcription factor 6), and IRE1 (inositol-requiring element 1). These three molecules are held in an inactive state by binding to a molecular chaperone, BiP on the luminal side of the ER. BiP also known as GRP78 and Hspa5 is an ATPase and member of the heat shock 70 family of proteins that binds preferentially to nascent and misfolded

proteins. Perturbation of ER homeostasis by events such as reduced energy, changes in calcium flux, redox changes, ischemia, hyperhomocysteinemia, viral infections, mutations (Kaufman 2002; Ron 2002), and sleep deprivation (Naidoo 2009) leads to protein misfolding. When this occurs, BiP dissociates from PERK, IRE1, and ATF6 to bind to the misfolded proteins and assist in their refolding or to escort these proteins out of the ER for degradation. The dissociation of BiP from these three molecules (PERK, IRE1, and ATF6) leads to their activation and that of three respective signaling cascades described below that transduce the ER stress signal to the cytosol and nucleus.

3.3.1 PERK Activation Leads to Attenuation of Protein Translation and an Antioxidant Response

PERK "type I transmembrane serine threonine kinase" is found in most cells that is activated upon dissociation from BiP. Activated PERK phosphorylates the translation initiation factor eIF2α that in turn forms a stalled 43S ternary complex, which in general decreases the translation of most proteins. The attenuation in protein translation serves to reduce the client protein load and stress within the ER. However, some proteins having internal ribosomal entry sites (IRES), such as ATF4, which modulate the expression levels of pro-survival genes associated with amino acid metabolism, protein folding, redox balance, and autophagy (Ameri and Harris 2008) and chaperones such as BiP and GRP94 are generally translated more efficiently (Harding et al. 2000), and hence their transcript and protein levels actually increase as is observed following sleep deprivation (Cirelli et al. 2004; Terao et al. 2006; Naidoo et al. 2005, 2008, Mackiewicz et al. 2007). Activation of the PERK pathway with sleep loss has been demonstrated in the cerebral cortex of mouse brain (Naidoo et al. 2005, 2008) and within Drosophila brain (Brown et al. 2014). The levels of PERK transcript remain high during wakefulness compared to sleep in the cerebellum of rat brain (Cirelli et al. 2004). Also, the PERK branch of the UPR modulates the expression of various microRNAs, which may in turn attenuate protein translation or protein synthesis (Behrman et al. 2011). Inducing ER stress also causes PERK to phosphorylate nuclear factor-E2-related factor 2 (Nrf2), a molecule that plays a significant role in the adaptive stress response to oxidative stress (He et al. 2001; Itoh et al. 1999; Venugopal and Jaiswal 1996) and xenobiotic detoxification (Motohashi and Yamamoto 2004). Nrf2 is involved in regulation of the inducible expression of ARE-containing target genes, for example, enzymes involved in glutathione biosynthesis and chemical detoxification (Chan et al. 2001; Ishii et al. 2000), which are induced during the UPR. PERK/Nrf2 translocation into the nucleus leads to the upregulation of genes involved in redox maintenance (Cullinan et al. 2003).

3.3.2 *IRE1 Activation Leads to Upregulation of Chaperones, ER Expansion, and Degradation of Transcripts and Misfolded Proteins*

Activated IRE1α which has both endoribonuclease and kinase activities removes an intron from the mRNA which encodes an UPR-specific transcription factor, X-box-binding protein (XBP) 1, and generates a spliced variant "xbp1s." Spliced xbp1 encodes XBP1 (a potent transcriptional transactivator of genes), which regulate the ER expansion, protein maturation, protein folding and transportation, and degradation of misfolded proteins from the ER (Calfon et al. 2002; Lee et al. 2002, 2003; Yoshida et al. 2001, 2003). Activation of IRE1 ribonuclease activity through xbp1 mRNA splicing has been observed in sleep-deprived fly brains (Brown et al. 2014; Naidoo et al. unpublished observations). Xbp 1 transcript levels have also been reported to increase in mouse brain (Mackiewicz et al. 2007; sleepgene.org). IRE1 is involved in the degradation of ER-bound mRNAs through a process called RIDD ("regulated IRE1-dependent decay"). It possibly reduces the protein influx and ER load of unfolded protein after prolonged UPR induction (Hollien and Weissman 2006; Pirot et al. 2007; Walter and Ron 2011). Specifically, mRNAs for secretory proteins that are predicted to be difficult to fold are degraded first (Hollien and Weissman 2006; Maurel et al. 2014). It is not known which transcripts are affected by sleep loss.

3.3.3 *Activated ATF6 Upregulates Chaperone Production*

ATF6 belongs to the ER stress transducers family, which encodes basic leucine zipper (bZIP) transcription factors, such as ATF6α, ATF6β, LUMAN (also known as CREB3), old astrocyte specifically induced substance (OASIS) (also known as CREB3L1), BBF2 human homologue on chromosome 7 (BBF2H7) (also known as CREB3L2), cyclic AMP-responsive element-binding protein hepatocyte (CREBH) (also known as CREB3L3), and CREB4 (also known as CREB3L4). When ER is under stress, ATF6 dissociates from BiP and is exported to the Golgi complex where it is cleaved by site-1 protease (S1P) and S2P releasing its cytosolic domain which is a potent transcription factor. ATF6α (a 50 kDa cleaved product) then enters cell nucleus and binds to the ER stress response element CCAAT(N)9CCACG (Yoshida et al. 1998) increasing the transcription of chaperones and several other ER proteins such as BiP, GRP94, CHOP, XBP-1, PDI (Protein disulfide isomerase), and HERP (hyperhomocysteinemia-induced ER stress-responsive protein) (Okada et al. 2002; Yoshida et al. 1998).

3.3.4 *Increased Transcription of ATF6 and XBP1 Targets with Sleep Loss and Recovery Sleep*

Several molecular chaperones besides BiP are also increased in the brain following sleep loss. ERP72, GRP94, HSP27, HSP70-1, and HSP84 mRNA levels are all increased after sleep deprivation in the cortex, hypothalamus, basal forebrain, cerebellum, and medulla, whereas with sleep recovery, the increased mRNA levels were only observed in the cortex and medulla (Terao et al. 2006). These chaperones are downstream targets of UPR transcription factors XBP1 and ATF6. The levels of other UPR-specific transcripts such as DNA-J, a co-chaperone of BiP, calreticulin, caspase-9, ATF4, ATF6 (Mackiewicz et al. 2007; sleepgene.org), and ERo1L (Williams et al. 2007) also changed with sleep deprivation. Several UPR activated pro-inflammatory molecules are also induced by sleep deprivation, including NF-κB and JNK (Williams et al. 2007).

3.4 Inflammatory and Pro-apoptotic Signaling Are Observed with Sleep Loss

The ER stress signal turned on during acute sleep loss is initially adaptive and turns maladaptive with sustained stress. Prolonged stress leads to inflammatory signaling that if not resolved leads to apoptosis. UPR signaling combines with several components of other well-known stress responses at a series of bidirectional cross talk points (Dufey et al. 2014). IRE1α activation recruits the adaptor protein TRAF2 (TNF receptor-associated factor 2) and engages "alarm" genes, which in turn activates the apoptosis signal-regulating kinase 1 (ASK1, also known as MAP3K5) pathway, and its downstream target JUN N-terminal kinase (JNK) (Hetz et al. 2011; Hu et al. 2006; Urano et al. 2000). NF-kappa B (NF-κB), which is also known to play a role in sleep (Kuo et al. 2010; Kuo and Williams 2014), is increased during the ER stress by two different ways: (i) The level of I kappa K (IKK) which has a shorter half-life is decreased in response to the attenuation in protein translation, which changes the stoichiometric ratio of NF-κB/IKK and releasing NF-κB for its translocation to the nucleus (Zhang and Kaufman 2008); (ii) I kappa B (IKB) kinase is recruited by the IRE1-TRAF2 complex, which phosphorylates IKB leading to its degradation (Hu et al. 2006).

Activated IRE1α also triggers JNK, a crucial pro-apoptotic signal. Its mechanism of action during ER stress is however not clearly known. IRE1α–JNK signaling can also trigger macro-autophagy that is induced by ER stress and nutrient starvation by activating beclin 1 (Hetz et al. 2011; Hu et al. 2006; Urano et al. 2000), an essential autophagy regulator. IRE1α also engages pathways involving p38, extracellular signal-regulated kinase (ERK), and nuclear factor-κB (NF-κB) through the binding

of distinct adaptor proteins (Nguyen et al. 2004; Hu et al. 2006). A growing number of studies have revealed that knocking down components of the JNK signaling pathway reduce sleep. For example, flies that lack an activator of JNK, *Tak1* (transforming growth factor β-activated kinase (Delaney et al. 2006), show reduced daily sleep (Williams et al. 2007). A homolog of mammalian JNK in *Drosophila*, Basket (bsk), is a sleep-promoting molecule. Blocking the expression of bsk in neurons through RNAi using the elav-GAL4 driver decreases total sleep, and a similar effect is mimicked by a bsk knockdown in the mushroom bodies (Takahama et al. 2012).

Sustained activation of the UPR leads to upregulation of one of the key UPR pro-apoptotic players, termed C/EBP-homologous protein (CHOP, also known as GADD153). CHOP which is controlled by the PERK–ATF4 axis activates the expression of several pro-apoptotic factors including Tribbles 3, GADD34, and DR5 and promotes both the transcription of BIM and the downregulation of the anti-apoptotic factor Bcl-2 (Tabas and Ron 2011; Hetz 2012). CHOP transcript has been found to be upregulated in the cerebral cortices of rats (Cirelli and Tononi 2000) and mice brain (Mackiewicz et al. 2007; Naidoo et al. 2008) following sleep deprivation suggesting that several hours of sleep loss does in fact trigger the pro-apoptotic arm of the UPR. Whether or not this leads to cell death is not known but it does indicate that neurons are under stress and that cytoprotective signaling is diminished.

The data on whether sleep loss leads to oxidative stress in neurons is mixed. Sleep loss has been shown to increase pro-inflammatory cytokine interleukin-1β mRNA levels in the brain (Taishi et al. 1998). Gopalakrishnan et al. have reported that there are no evidence of oxidative damage to either lipids or proteins in the brain or the peripheral tissues including the liver and skeletal muscle after sleep deprivation (Gopalakrishnan et al. 2004). Similarly, D'Almedia et al. have reported that the activity of antioxidant enzymes superoxide dismutase, glutathione peroxidase, catalase, or malondialdehyde did not change after sleep deprivation in rats (D'Almeida et al. 1997). Some studies, however, suggest that SD may create conditions associated with oxidative stress, as the glutathione levels in whole rat brain decreases (D'Almeida et al. 1998). Also, the activity of SOD in the hippocampus and brain stem significantly decreases after sleep deprivation (Ramanathan et al. 2002). A subsequent study involving prolonged sleep deprivation of mice for 72 h using the "flower pot" or platform methods has observed a significant increase in oxidative stress in the hippocampus as the lipid peroxidation and ratios of oxidized to reduced glutathione levels significantly increased (Silva et al. 2004).

3.5 Aging Exacerbates Sleep Loss-Induced Cellular Stress

Aged animals in general show more fragmented sleep (Welsh et al. 1986; Shiromani et al. 2000) and wake (Naidoo et al. 2011) with shorter bout durations and increased numbers of bouts. At the same time, several studies indicate increased expression of

ER stress molecules in bulk brain tissue and neurons of animals examined during baseline sleep in the absence of sleep deprivation (Naidoo et al. 2011, 2008; Brown et al. 2014). Accompanying this increase in ER stress molecules, there is a loss of the adaptive UPR to sleep deprivation and increased inflammatory/pro-apoptotic signaling (Naidoo et al. 2008). The UPR is impaired in aged mice cerebral cortices (Naidoo et al. 2008) with no upregulation of the cytoprotective chaperone BiP. There is instead an increase in pro-apoptotic markers such as CHOP, GADD34, and caspase 12 in these mice cortices. Similar observations have been made in aged Drosophila brains; basal BiP expression is decreased accompanied by increased activation of the PERK pathway (Brown et al. 2014). Wake-active neurons show a significant activation of the PERK pathway and ER stress in aged mice compared to the young ones (Naidoo et al. 2011). In this study, we have observed that aged mice demonstrated wake instability and altered wake responses to novelty along with ER stress in wake-related orexinergic and noradrenergic neurons (Naidoo et al. 2011). The ER stress response was clearly evident in orexin and noradrenergic neurons as we observed the presence of activated phosphorylated PERK, nuclear translocation of CHOP, and increased GADD34 expression. The specific wake associated impairments in aged mice identified were consistent with orexinergic and noradrenergic neuronal injury.

3.5.1 Noradrenergic Neuronal Injury

Whether these injuries contribute to neuronal loss is not known as studies indicate that the number of neurons in LC remains unaltered during healthy aging (Mouton et al. 1994; Ohm et al. 1997). However, studies involving humans as well as animals have clearly demonstrated that the connectivity, expression profiles, and functions of these LC neurons are altered over time. In humans, LC neuromelanin levels remain high during the middle age and decrease in aged subjects, which may alter neuronal susceptibility to oxidative stress (Shibata et al. 2006). In addition, it has been reported that norepinephrine reuptake from the axon terminals in the cortex and mRNA levels of norepinephrine transporter (NET) decreased in aged animals (Shirokawa et al. 2003; Shores et al. 1999; Zhu et al. 2005). Levels of mRNA of dopamine β-hydroxylase (DBH), an enzyme which converts dopamine to norepinephrine, also decline in LC with age (Zhu et al. 2005).

3.5.2 Orexin Neuron Injury

Along with a loss of wake consolidation with aging (Foley et al. 2007), the numbers of orexinergic neurons decreased substantially in aged rats (Kessler et al. 2011) and mice (Brownell and Conti 2010), and interestingly, the remaining neurons demonstrate the decreased signs of activation in response to sleep deprivation (Naidoo et al. 2011).

3.6 REM Sleep Loss, Mitochondrial Stress, and Neuronal Loss

REM sleep disturbances are common in psychiatric disorders and neurodegenerative diseases. The presence of sleep fragmentation concomitant with sleep disturbance (reduced REM sleep and frequent and prolonged waking throughout the night) is commonly associated with Parkinson's disease (Mandel et al. 2010). It is thought that these disturbances or disruptions in REM sleep may be predictive of neuronal dysfunction and prodromal markers of neurodegeneration (Fulda 2011; Mandel et al. 2010). REM sleep deprivation has been shown in animal models to affect neuronal cytomorphology and structural proteins leading to neuronal apoptosis and loss (Majumdar and Mallick 2005; Biswas et al. 2006). These effects were shown to be mediated by elevated noradrenaline levels in the brain during REM sleep loss (Ranjan et al. 2010). It has recently been shown that REM sleep deprivation-mediated-induced apoptosis occurs by the activation of the mitochondrial intrinsic pathway which is initiated by elevated level of noradrenaline acting on alpha1 adrenoreceptor present on neurons (Somarajan et al. 2016). The mitochondrial-mediated intrinsic pathway is precisely modulated by a balance between the pro-apoptotic (Bad, Bax, and Bak) and anti-apoptotic (Bcl-2 and Bcl-x) members of the Bcl-2 family. The pro-apoptotic Bcl-2 members, which consist of Bak and Bax, undergo conformational changes in response to ER stress, which results in the release of calcium from the ER lumen (Zong et al. 2003). CHOP, a pro-apoptotic member of the ER stress signaling pathway, inhibits anti-apoptotic Bcl-2 and promotes the translocation of Bax to the mitochondria (McCullough et al. 2001). CHOP has been shown to be increased especially in aged animals in response to sleep loss (Naidoo et al. 2008). These components also affect the mitochondrial membrane leading to the release of cytochrome c and activation of mitochondrial-mediated caspases (Nechushtan et al. 1999; Wolter et al. 1997). Somarajan et al. (2016) demonstrate that 6 days of REM sleep deprivation by the flower pot method leads to increased cytochrome c release downstream of noradrenergic activity and that this is accompanied by elevated levels of BAD, apoptosis protease-activating factor-1 (Apaf1), and caspases 3 and 9. Given the link to Parkinson's disease, it is likely that activation of ER pro-apoptotic signaling and mitochondrial stress is the mechanism by which chronic REM sleep loss contributes to neuronal stress and loss.

3.7 Chronic Sleep Disturbances and Neuronal Loss

Wake-active neurons are those that remain quiescent during sleep and are activated during wakefulness are particularly vulnerable to sleep loss and stress. Wake-active neurons which fire at high frequency during wake and low frequency during sleep include orexinergic (de Lecea and Huerta 2014), cholinergic (Platt and Riedel 2011), histaminergic (Huang et al. 2001), noradrenergic (Gonzalez and Aston-Jones 2006),

serotonergic (Monti 2011), and dopaminergic (Lu et al. 2006) group of neurons. Orexin and noradrenergic LC neurons have been shown to experience cellular/ER stress even in the absence of sleep deprivation; about 40% of these neurons in young mice exhibit PERK activation (Naidoo et al. 2011). Brainstem LC neurons in particular are highly susceptible to sleep disturbances. In cats, REM sleep deprivation during postnatal day 42–49 causes death of over half of LC neurons, and the size of the remaining LC cells considerably decreases (Shaffery et al. 2012). The number of LC neurons in mice decreases after intermittent hypoxia, which models interruptions in breathing during sleep apnea as well as after chronic sleep deprivation (Zhang et al. 2014; Zhu et al. 2007). LC neurons when subjected to short-term sleep loss respond by upregulating antioxidant enzymes do not evidence a similar response during chronic sleep loss (Zhang et al. 2014). In the chronic sleep loss paradigm developed by Sigrid Veasey's group exposing mice to 8 h of sleep loss over three consecutive days followed by 4 days of undisturbed sleep, LC neurons displayed no upregulation of antioxidant enzymes but instead exhibited increased reactive oxygen species (ROS) (Zhang et al. 2014). SirT3 (sirtuin type 3), a major mitochondrial deacetylase enzyme, was increased following acute but not chronic sleep loss leading to hyperacetylation of mitochondrial proteins (Zhang et al. 2014). This resulted in accumulation of lipofuscin and extreme oxidative stress. The most dramatic outcome in this chronic sleep loss paradigm was the 25–30% loss of LC neurons. This chronic sleep loss paradigm was extended to 4 weeks to ascertain whether longer durations of sleep loss would incur more injury and whether other neuronal populations would be susceptible. An extension of the chronic sleep loss paradigm to 4 weeks resulted in a 40% loss of neurons with no recovery of neuron numbers with 1 month of rest supporting the idea of irrecoverable neuron loss (Zhu et al. 2016). Reasons for LC susceptibility to stressors such as sleep loss are unclear, but several hypotheses have been proposed. High levels of NADPH oxidase may play a role in contributing to oxidative injury (Zhu et al. 2007; Zhan et al. 2005). Further, latest evidence from slice recordings demonstrate that LC neurons experience intense mitochondrial oxidant stress due to basal calcium oscillations (Sanchez-Padilla et al. 2014). The sirtuins, SirT1 and SirT3 which have been shown to decline in the brain with aging (Guarente and Kenyon 2000; Haigis and Guarente 2006; Someya et al. 2010), were found to be diminished in both LC and orexin neurons with chronic sleep loss (Zhu et al. 2016) suggesting that redox dyshomeostasis may be a contributing factor to neuronal stress and loss. These declines in sirtuins also persisted into the 1 month rest recovery period suggesting lasting effects of chronic sleep loss. In this same study, the authors also examined the effect of chronic sleep loss on orexinergic neurons and found a similar 40% loss of those neurons. At the same time, lasting sleep/wake changes were also observed following the chronic sleep loss intervention; mice displayed less sleep during the normal lights on sleep period and more sleep during the active lights off period (Zhu et al. 2016). These changes in sleep are similar to that observed during aging.

Fragmentation of sleep is often experienced by individuals with sleep disorders such as sleep apnea as well as during aging. Similar to chronic sleep loss the Veasey group found that both LC and orexin neurons suffered neural injury and loss during

sleep fragmentation (Zhu et al. 2015). They also reported increased oxidative stress in LC neurons accompanied by reduced SirT3 expression (Zhu et al. 2015). Chronic sleep fragmentation has also been shown to cause decreased activation of orexinergic neurons to hypercapnia and abridged orexinergic neuronal projections to the cingulate cortex (Li et al. 2014). An earlier study found that chronically sleep-deprived mice (12 h a day for 7 days) lost 24% orexinergic neurons in the lateral hypothalamus (Obukuro et al. 2013). This loss of orexinergic neurons was associated with S-linked nitrosylation of the critical foldase and ER chaperone protein disulfide isomerase (PDI). It has also been found that this particular protein modification plays an essential role in the progression of neurodegenerative diseases related to protein misfolding (Halloran et al. 2013; Uehara et al. 2006).

3.7.1 Metabolic Effects of Neuronal Stress

A recent study from the Gozal group showed that chronic sleep fragmentation also induced temporal changes in ER stress in the hypothalamic brain area, across the three major UPR pathways that led to leptin resistance (Hakim et al. 2015). There was an increase in cleaved ATF6 expression, splicing of XBP1 mRNA indicative of IRE1 activation and induction of the PERK pathway evidenced by increased p-eIF2α expression. The UPR chaperones BiP, HSP70, and HSP90 also displayed elevated expression levels in hypothalamic cellular extracts after sleep fragmentation compared with sleep control conditions. This study also found that chronic sleep fragmentation leads to sustained ER stress and induction of leptin resistance (Hakim et al. 2015) suggesting a mechanism by which sleep impacts upon metabolism.

3.8 Summary and Concluding Remarks

The importance of sleep in metabolism and in learning and memory has been ascertained. As outlined in this chapter, both acute and chronic sleep loss have been shown to have an effect on neuronal health and brain function (Fig. 3.2). Various animal studies have now offered the reasonable mechanistic bases for effects of sleep disturbance in onset or progression of neurodegenerative disease. Studies in mice suggest that β-amyloid levels in interstitial fluid increased due to sleep deprivation (Kang et al. 2009; Musiek et al. 2015), and one of the key functions of sleep may be to enhance clearance of these potential toxic metabolites including β-amyloid from the brain (Xie et al. 2013). Injury and loss of LC neurons occurring as a result of chronic sleep loss also have broad implications for the progression of Alzheimer's and other neurodegenerative diseases. Furthermore, it has been reported that damage of the LC neurons in the Alzheimer's disease (AD) and Parkinson's disease (PD) patients is higher as compared to the regions of forebrain and substantia nigra (Zarow et al. 2003). LC neuron lesions in mouse models of Alzheimer's

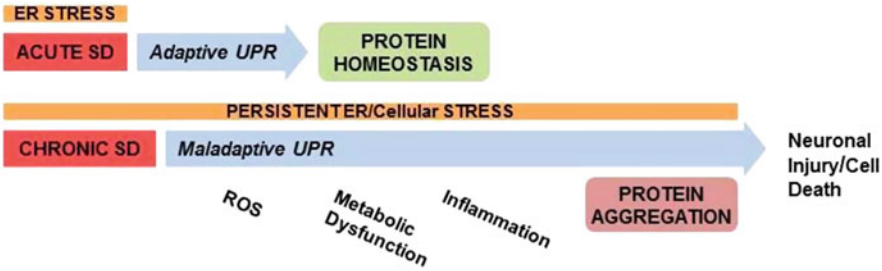

Fig. 3.2 Scheme/model showing the effect of acute and chronic sleep loss on adaptive and maladaptive UPR signaling. Downstream processes that have been demonstrated to induce neuronal injury and loss are also shown

disease increase plaque burden as well as tau hyperphosphorylation, while replenishing norepinephrine mitigates deficits (Heneka et al. 2006; Kalinin et al. 2012). A large number of neurons in LC are lost in AD, PD, and dementia with Lewy bodies (DLB) patients (Brunnstrom et al. 2011) and to a lesser extent in frontotemporal lobar degeneration (FTLD) (Brunnstrom et al. 2011). Furthermore, morphological and histological changes occur in LC of amyotrophic lateral sclerosis (ALS) patients as well (Hoogendijk et al. 1995; Iwanaga et al. 1997). All of the data and observations presented underscore the idea that inadequate sleep or sleep loss in the elderly, who usually experience sleep disturbances, could further worsen an already-impaired protective response to protein misfolding in the aging cells. Many of the aging-related diseases like AD and PD are after all characterized by protein misfolding. All these studies suggest that loss of sleep and wake consolidation often precedes and predicts neurodegenerative disease (Abbott et al. 2005; Lim et al. 2013; Schenck et al. 2013). Therefore, non-pharmacological (Wennberg et al. 2013) or pharmacological (Lyseng-Williamson 2012; Wennberg et al. 2013) approach/s for sleep therapies should be considered that can decrease the chances of disease onset by preserving the wake-active neuronal systems in the elderly population.

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Chapter 4
The Role of Sleep in Homeostatic Regulation of Ionic Balances and Its Implication in Cognitive Functions

Fayaz Ahmad Mir, Sushil K. Jha, and Vibha M. Jha

Abstract Several studies have suggested that physiological sleep is an indispensable part of the system. It is, however, not known what sleep does to our brain and body. Sleep helps to modulate transcription and translational processes, synaptic neurotransmission, metabolic processes, detoxification, restitution, proliferation, thermoregulation and neuro-immuno-endocrine information, stress reactions, emotional fluctuations, growth, timekeeping, and strategy for survival. In addition, evidences suggest that sleep could be involved in the maintenance of inter- and intracellular microenvironments. Sleep may modulate the homeostatic regulation of (a) acid-base balance, (b) biological buffer system, and (c) ionic/electrolytic balances. We have proposed earlier that one of the essential functions of REM sleep could be to maintain normal bodily CO_2 level during sleep. The elevated bodily CO_2 level during prolonged vigilant states can adversely alter the cellular ionic milieu. Therefore, it is essential that the level of CO_2 must remain within physiological limits, and sleep seems to play an essential role in the maintenance of physiological CO_2 level. Furthermore, sleep may also be playing an essential role in maintaining homeostatic balance of several ions such as iron, calcium, potassium, sodium, zinc, magnesium, etc. In this chapter, we discuss the role of sleep in the maintenance of ionic and acid-base balances. We have also addressed how the chronic and acute sleep loss can cause ionic imbalances leading to cellular distress. Further, we have attempted to highlight the influence of ionic homeostatic dysregulation on cognitive performances.

Keywords Acid-base balance · Energy homeostasis · Learning and memory · Respiratory acidosis · NREM sleep · REM sleep and sleep deprivation

F. A. Mir
School of Life Science, Jawaharlal Nehru University, New Delhi, India

S. K. Jha · V. M. Jha (✉)
Sleep Research Laboratory, School of Life Sciences, Jawaharlal Nehru University, New Delhi, India

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4.1 Introduction

How sleep should be defined is still debatable. Nonetheless, it is considered to be a reversible behavioral state, during which, the perception of the sensory stimuli, consciousness, and activity of voluntary muscles remains subdued (Carskadon and Dement 2005). Electrophysiologically, it has been characterized broadly into two stages: non-rapid eye movement (NREM) and rapid eye movement (REM) sleep (Aserinsky and Kleitman 1953). Two distinct sleep states have been characterized only in terrestrial mammals and birds (Madan and Jha 2012b), and it is unclear why these distinct sleep states have evolved only in phylogenetically advanced animals. Although several studies have suggested that physiologically, sleep is an indispensable part of the system, what sleep does to our brain and body is still under study.

Several theories have been put forward regarding the functions of sleep. It has been proposed that sleep helps to modulate transcription and translational processes at the molecular level; synaptic neurotransmission at the subcellular level; metabolic processes, detoxification, restitution, and proliferation at the cellular level; thermoregulation and neuro-immuno-endocrine information processing at the physiological level; stress reactions and emotional fluctuations at the psychological level; immune and host defense responses at the pathological level; pregnancy and lactation at the reproductive level; growth and timekeeping at the whole body level; and strategy for survival at the evolutionary level (Inoue et al. 1995; Cirelli 2002, 2013; Guzman-Marin et al. 2003; Madan and Jha 2012a, b, 2014; Vecsey et al. 2012). The available knowledge thus allows us to believe that sleep has multidimensional functions.

Some current evidence suggests that sleep could be involved in the maintenance of inter- and intracellular microenvironments. Sleep may modulate the homeostatic regulation of (a) acid-base balance, (b) biological buffer system, and (c) ionic/electrolytic balances. We have proposed earlier that one of the essential functions of REM sleep could be to maintain normal bodily CO_2 level during sleep (Madan and Jha 2012a). In addition, it has been found that moderate increase in ambient CO_2 level induces NREM sleep (Fraigne et al. 2008). The elevated bodily CO_2 level during prolonged vigilant states can adversely alter the cellular ionic milieu. Therefore, it is essential that the level of CO_2 must remain within physiological limits, and sleep may be playing an essential role in the maintenance of physiological CO_2 level (Madan and Jha 2012a). In this chapter, we discuss the role of sleep in the maintenance of homeostatic ionic and acid-base balances. We have also addressed how the chronic and acute sleep loss can cause ionic imbalance and cellular distress. Further, we have attempted to highlight the influence of ionic homeostatic dysregulation on cognitive performances.

4.2 Acid-Base Balance

Before we discuss the role of sleep in homeostatic regulation of acid-base balance, it would be imperative to know about the ionic regulatory machinery. One of the most essential homeostatic mechanisms is the one regulating the concentration of hydrogen ions (pH) in the body fluids. Biological pH is tightly regulated by various mechanisms, such as the changes in the respiratory rate, the buffering capacity of the protein molecules present in the body fluid, and the buffer systems (phosphate and bicarbonate buffers) that exist in our body. The various types of machinery are essential because every cellular reaction occurs at an optimal pH. The structure and functions of proteins present in the intracellular and extracellular compartments are susceptible to pH alterations. Changes in body pH may lead to pathophysiological conditions such as stroke, seizures, pain, anxiety, meningitis, tumors, trauma, severe anemia, hepatic and cardiac failure, etc. (Das 2003). Therefore, the pH of extracellular fluids must be tightly controlled within narrow ranges for optimal cellular function.

The alterations in bodily pH occur mainly because of two etiological factors: respiratory acidosis/alkalosis and metabolic acidosis/alkalosis. Hydrogen/hydroxyl ions reversibly bind to various extracellular and intracellular buffering agents, for example, proteins (hemoglobin), bicarbonate buffer, phosphate buffer, etc. and resist pH change (Stewart 1978). The pH of the blood mainly decreases because of either (a) high levels of CO_2 production through metabolism or (b) hypoventilation. Increase in carbon dioxide (CO_2) levels in the body raises the hydrogen ion (H^+) concentration and decreases the pH of blood. The increased CO_2 level in the body stimulates central respiratory centers, which increase the breathing rate at the first place to remove excess CO_2. The increased breathing rate expels more CO_2 from the body, which ultimately depletes H^+, and finally, the blood pH gets back to normal. This is how our sensitive respiratory system is involved in the regulation of H^+ concentration (Das 2003).

4.2.1 Sleep and Respiratory Acidosis

Sleep plays an essential role in preventing respiratory acidosis. Respiratory acidosis is usually caused by the alveolar hypoventilation, which increases arterial partial pressure of carbon dioxide, thereby decreasing blood pH (Böing and Randerath 2015). Although blood pH is maintained within tight physiological limits, it varies across day and night and exhibits diurnal alterations. It has been reported that the pH of blood increases after meal and decreases during sleep (Rune and Lassen 1968). In addition, it has been found that ventilation rate and blood pH remain at a lower level during NREM sleep (McKay et al. 2010; Madan and Jha 2012a). Hypercapnia (high CO_2 level) has been observed during sleep prior to wakefulness, and also the minute ventilation rate decreases from wakefulness to NREM sleep (Böing and Randerath

2015). Besides the bodily changes in CO_2 level across sleep-wake states, the ambient change in CO_2 level also influences sleep pattern. For example, mild increase in CO_2 level (2%) in the surroundings induces total sleep with a concomitant increase in REM sleep frequency, while high level of CO_2 (6–8%) in the ambience significantly decreases total sleep amount (Fraigne et al. 2008). Rhythmic changes in CO_2 and blood pH level across sleep-wakefulness and the influence of ambient CO_2 level on sleep suggest that there would be a close link between the chemosensory and sleep machineries and can affect each other through some common pathways.

The central chemosensory system is located in the brainstem medullary area (Squire et al. 2013). Neurons in the brainstem nuclei such as the locus coeruleus (LC), retrotrapezoid nucleus (RTN), solitary tract nucleus (NTS), and dorsal raphe nucleus (DRN) sense the changes in hydrogen ion concentration in the extracellular fluids and accordingly stimulate the breathing centers. This in turn alters the breathing rates to bring the altered level of CO_2 in a normal range (Bruce and Cherniack 1987; Arita et al. 1989; Nattie and Li 2009; Squire et al. 2013). The central chemosensory system modulates breathing rate (hyper- or hypoventilation) depending upon the changes in the pH of extra- or intracellular fluid through the inspiratory and expiratory neurons and also rhythm generating brainstem neurons (Taylor et al. 1999; Nattie and Li 2009; Smith et al. 2015). Interestingly, the chemosensory circuitries, which involve the LC, DRN, etc., are also a part of the ascending reticular arousal system (Jha and Mallick 2011; Madan and Jha 2012a). The DRN and LC areas contain wake-active neurons, which are maximally active during wakefulness, and their firing rate slows down during transition from wake to NREM sleep. They remain moderately active during NREM sleep but cease firing during REM sleep (for review see (Jha and Mallick 2011; Madan and Jha 2012a). The expression patterns of NREM and REM sleep significantly alter with the LC and DRN ablation (McGinty and Harper 1976; Schwartz et al. 2016). In addition, DRN and LC lesion in adult animals or early during the prenatal period reduces CO_2-mediated induction of physiological responses (Nattie and Li 2009). These studies further suggest that the two primary brainstem nuclei, the LC and DRN, play an essential role in the regulation of sleep as well as chemoreception.

Furthermore, the brainstem damage because of acute infarction, stroke, etc. causes sleep-disordered breathing (SDB) (Brown et al. 2014). One of the examples of SDB is obstructive sleep apnea (OSA), which is primarily characterized by repetitive episodes of complete or partial obstruction of airflow during sleep. Interestingly, it has been found that serotonin and norepinephrine levels are altered in OSA patients (Ozaki et al. 1986; Cui et al. 2012). The diaphragm and genioglossus respiratory muscles help in normal breathing, and the phrenic nerve through the cervical C3, C4, and C5 areas innervates these diaphragm muscles. The nerve conduction velocity of the phrenic nerve is considered a good indicator of diaphragm function (Cui et al. 2012). An altered activity of the diaphragm and genioglossus muscles has been found in OSA patients (Cui et al. 2012). Although it is not known how the activity of these muscles alters, it is believed that the altered level of serotonin and norepinephrine in OSA patients could be associated with breathing disorder (Ozaki et al. 1986; Mahamed and Mitchell 2007; Cui et al. 2012). Thus, it

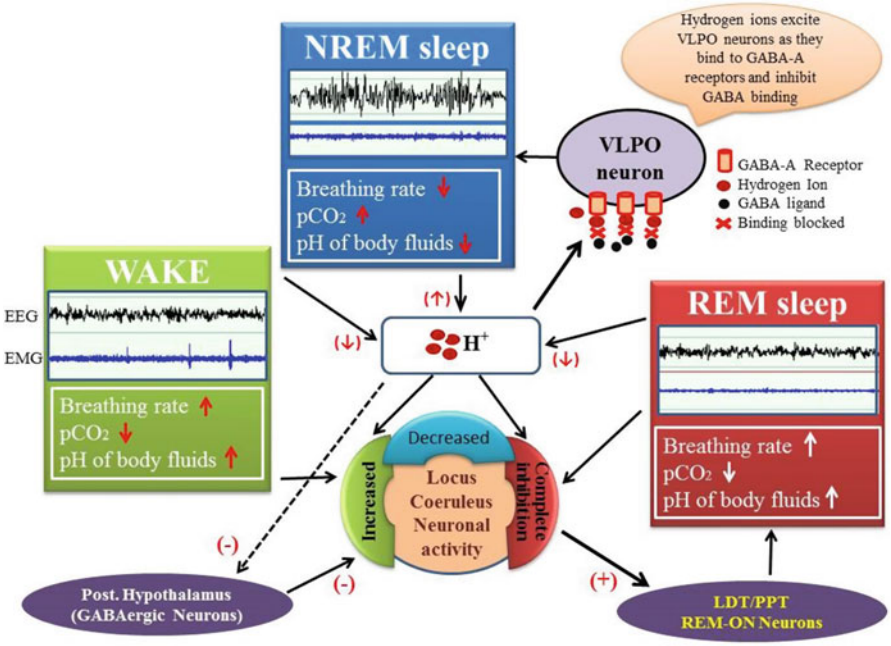

Fig. 4.1 The proposed model explains the changes in the hydrogen ion level across sleep-wake cycle and influence of increased hydrogen ion concentration on NREM sleep and REM sleep generation. *Abbreviations*: *LDT* laterodorsal tegmentum, *PPT* pedunculopontine tegmentum

seems that the DRN and LC not only modulate sleep and chemoreception but are also associated with the pathophysiology of sleep-related breathing disorders.

The brainstem nuclei, such as the LC, have a high proportion (>80%) of wake and chemosensitive neurons (Aston-Jones and Bloom 1981; Pineda and Aghajanian 1997). These neurons are highly active during wake and normocapnia, but the firing rate significantly alters with the change in behavioral state or CO_2 level (Madan and Jha 2012a). For example, mild hypercapnia excites the LC neurons, while acute hypercapnia hyperpolarizes LC neurons (Dean et al. 2001). It is not known if the wake- or REM sleep-related neurons in the LC are also chemosensitive in nature, but it appears that some of the neurons may be participating in both the functions. The REM-OFF neurons cease their activity during REM sleep, but it is not known how REM-OFF neurons become hyperpolarized during REM sleep. One of the possible reasons that can be attributed to the alteration in the firing rate could be the changes in the H^+ ion concentration in and around the LC neurons during sleep. It has been observed that the minute ventilation rate reduces and upper airway resistance increases at NREM sleep onset, which can increase H^+ ion concentration in the brain (Fig. 4.1) (McKay et al. 2010). An elevated H^+ ion concentration if sustained for a while during the stable and lengthy episodes of NREM sleep, it may switch off LC's REM-OFF neurons for REM sleep genesis. Therefore, it is likely that the elevated CO_2 level within a set range during stable NREM sleep episodes may

hyperpolarize REM-OFF neurons. We have proposed that one of the functions of REM sleep could be to help prevent the induction of hypercapnia during sleep (Madan and Jha 2012a).

These studies suggest that chemoregulatory and sleep machinery are closely linked. An alteration in either system may influence the other. For example, sleep fragmentation alters blood pressure and heart rate variability (Carrington and Trinder 2008). Sleep deprivation may induce acid-base homeostatic imbalance (Madan and Jha 2012a). On the other hand, different ions may also influence sleep architecture (Held et al. 2002). There is a definite evidence suggesting that the two independent systems are closely linked. We will now highlight the possible role of sleep in the maintenance of ionic balances. We will also point out how sleep deprivation alters the cellular environment. Further, we will attempt to discuss the possible impact of alteration in cellular milieu on cognitive ability.

4.3 The Role of Sleep in Hemoglobin's H^+ Buffering Capacity

Almost all proteins can function as buffers. The positively charged amino groups and negatively charged carboxyl groups of amino acids of proteins can bind hydrogen and hydroxyl ions and thus function as buffers. In erythrocytes, carbonic anhydrase enzyme converts CO_2 and H_2O into carbonic acid (H_2CO_3), which is finally dissociated into H^+ and HCO_3^-. The liberated hydrogen ions are then buffered by hemoglobin. In the pulmonary capillaries, the conversion process is reversed, and CO_2 is formed from the H^+ and HCO_3^-, which is exhaled into the atmosphere. The buffering capacity of hemoglobin thus plays a vital role in the maintenance of blood pH within physiological limits.

Some studies suggest that altered sleep-wake pattern can affect the structural and functional properties of hemoglobin. It has been found that acute sleep loss (24 h) is associated with high level of glycated hemoglobin (HbA1c) (Kachi et al. 2011). Under the persisted hyperglycemic condition, hemoglobin binds to glucose molecules. Once glucose molecule binds to hemoglobin, it does not dissociate, and the hemoglobin remains glycated (Ye et al. 2016). Surprisingly, the high level of HbA1c is significantly correlated with chronic early morning awakening and poor sleep quality (Kachi et al. 2011). Kachi et al. (2011) have reported a high level of HbA1c in the blood of clinically insomniac as well as patients having milder forms of insomnia. Insomniac patients having a high level of HbA1c were not suffering from any other diseases such as diabetes, hypertension, etc. However, they have not observed any significant association between the level of HbA1c and altered sleep latency (Kachi et al. 2011). Hence, it was argued that high level of HbA1c might not have influenced sleep properties; instead, poor sleep quality would have altered the properties of hemoglobin.

Sleep deprivation can alter the properties of hemoglobin, but whether it affects the buffering capacity of hemoglobin is an intriguing question. It has been found that

24 h sleep deprivation affects the ventilatory response and bodily CO_2 level (Schiffman et al. 1983). Schiffman et al. (1983) have argued that a decline in hypercapnia-induced ventilatory response could be attributed to a decrease in ventilatory drive but not to the changes in lung mechanics (Schiffman et al. 1983). On the other hand, the high proportion of HbA1c has been observed in patients suffering from diabetes and kidney diseases (Shadman et al. 2013; Kang et al. 2015). Surprisingly, these patients were also diagnosed with altered ventilatory response to hypercapnia and ventilatory drive (Williams et al. 1984). Furthermore, structural and functional alteration has been observed in sugar-bound hemoglobin HbA1c (De Rosa et al. 1998). It has been observed that (a) the low-affinity conformation (or T-state) of HbA1c is destabilized by the chemical modification and (b) the "Bohr effect" is reduced with respect to that of native hemoglobin (HbA0) (De Rosa et al. 1998). The reduced Bohr effect in hemoglobin changes the acidic or alkaline nature of hemoglobin, which may affect its buffering capacity (Thom et al. 2013). Since the Bohr effect is reduced in the HbA1c, it can be assumed that it may have reduced the buffering capacity. Since early morning awakening or poor sleep quality causes glycosylation of hemoglobin, which may have an inadequate buffering capacity, it is possible that sleep modulates the ionic buffering properties of hemoglobin.

In addition, studies suggest that hematocrit value (percent RBC in the blood) is significantly high in severe OSA patients (Choi et al. 2006). Treating sleep apnea patients with continuous overnight positive airway pressure (CPAP) reduces the hematocrit value (Krieger et al. 1990). Abnormally poor sleep quality is manifested in sleep apnea patients (Macey et al. 2010), and CPAP treatment also improves sleep amount in these patients. These results further suggest that poor sleep quality may influence the blood dynamics and hemoglobin properties.

4.3.1 Sleep Deprivation and Changes in Protein Buffering Capacity

Based on the pH of extra-/intracellular fluid, the carboxyl and/or amine group side chains of amino acids in proteins can act as a proton donor or proton acceptor. At a normal body pH, most carboxyl groups exist as COO^- and can accept hydrogen ions, if the pH begins to drop. Similarly, histidine and cysteine amino acids have COOH at normal body pH and can donate hydrogen ion, if the pH begins to rise. This is how most proteins buffer acid or base and help regulate pH of the extracellular and/or intracellular compartments.

Changes in the level of specific proteins in the organelles under a particular situation, such as sleep deprivation, may influence the acid-base balance. Changes in proteome levels in the entire brain have been examined by using advanced quantitative proteomic technologies. It has been found that the level of nearly 10,000 proteins is altered after sleep deprivation. Surprisingly, the majority upregulated proteins were associated with mitochondria and energy metabolism (Ren et al. 2016). Furthermore, the mitochondrial uncoupling proteins UCP2 and

UCP3 also increased after sleep deprivation in the liver and skeletal muscle (Cirelli and Tononi 2004). The uncoupling proteins UCP2 and UCP3 are mitochondrial anion-carrier proteins, which play an essential regulatory role in the generation of reactive oxygen species (ROS) from the electron transport chain. The overproduction of ROS by the respiratory chain activates UCP2 and UCP3 proteins, which in turn augments proton leak from the mitochondrial membrane (Mailloux and Harper 2011). The alteration in the proton-motive force across the mitochondrial membrane influences proton gradient and ultimately mitochondrial pH (Dzbek and Korzeniewski 2008). Since the level of UCP2 and UCP3 proteins increases after sleep deprivation, which enhances proton leak across the mitochondrial membrane, suggesting that sleep deprivation may affect the proton-motive force and mitochondrial pH. Furthermore, the increased level of ROS production is also associated with an alteration in mitochondrial pH regulation and sleep deprivation (Ramanathan et al. 2002; Milner et al. 2007). It has been found that sleep deprivation significantly decreases the activity of superoxide dismutase (SOD) enzyme, and decreased SOD activity causes increased production of ROS (Ramanathan et al. 2002). On the other hand, it has been reported that the changes in ROS level influence the activity of Na^+/H^+ exchanger and thereby alter intracellular acidification (Milner et al. 2007). These results indicate that sleep deprivation causes an acid-base homeostatic imbalance at least at the organelle level, which could be attributed to sleep-deprivation-mediated changes at the proteome level.

4.4 Sleep and Electrolytic Ionic Balance

Sleep may also have a role in the maintenance of bodily electrolytic balance. Electrolytic ions such as sodium, potassium, chloride, bicarbonate, phosphate, magnesium, calcium, etc. are vital for cellular functioning and are required for various biochemical and enzymatic reactions. These ions are also necessarily required for efficient performance of several physiological processes, for example, neurotransmission, muscle contraction, heart function, etc. The excitable cells, such as neurons and muscle cells, require the movement of Na^+ and K^+ ions across the membrane to maintain and generate the membrane action potential. Interestingly, it has been observed that sleep deprivation causes electrolytic imbalances within the body, which ultimately lead to many pathophysiological conditions. Many reports suggest that sleep plays a vital role in the homeostatic regulation of ionic balances either directly or through modulation of neuroendocrine functions (Fig. 4.2).

The neuroendocrine system, which regulates bodily ionic balances, involves mineralocorticoid hormones. Aldosterone is one of the mineralocorticoid hormones, which is synthesized and released mainly by the zona glomerulosa cells of the outer layer of the adrenal gland. The adrenal gland releases aldosterone primarily in response to angiotensin II, which in turn induces sodium reabsorption by activating the apical epithelial sodium channel and the basolateral Na^+-K^+-ATPase pump in the

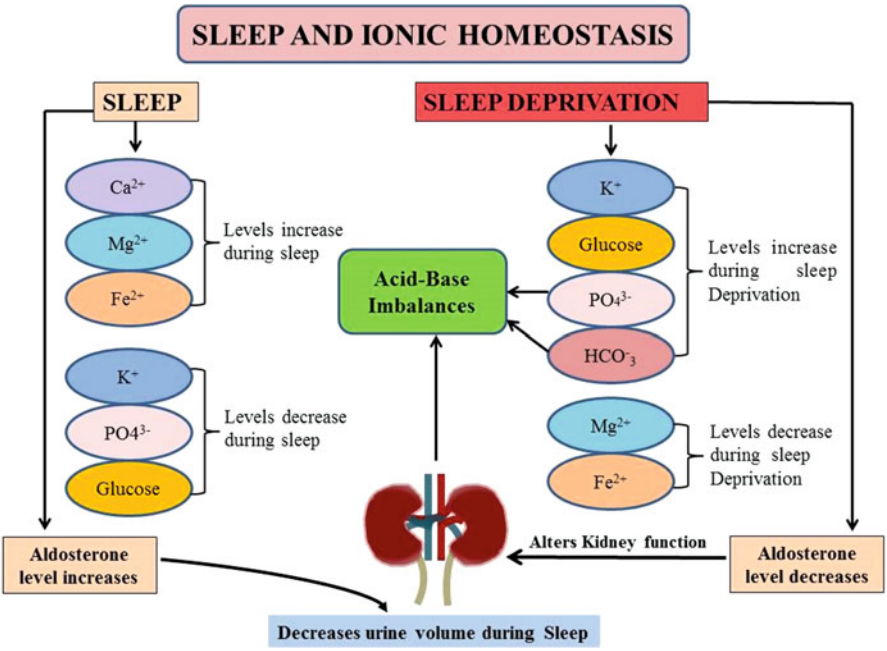

Fig. 4.2 Changes in the level of aldosterone and various other ions during sleep and sleep deprivation. Sleep possibly plays a major role in the maintenance of ionic and acid-base balances

distal nephron (Briet and Schiffrin 2010). Thus, it plays a significant role in the maintenance of sodium balance.

4.4.1 Aldosterone Release Is Augmented during Sleep

Interestingly, it has been observed that aldosterone secretion is modulated by two primary hormonal systems, i.e., the renin-angiotensin system and the adrenocorticotropic system. It has been reported that the peak release of aldosterone shows a synchronous pattern with cortisol peak, which occurred during late sleep and early morning hours (Katz et al. 1972). Furthermore, highest release of aldosterone (both high pulse amplitude and pulse frequency) has been observed during sleep and reduced release of aldosterone during sleep deprivation (Charloux et al. 1999). In addition, it has been found that among the two hormonal systems that influence aldosterone pulsatility, the renin-angiotensin system plays a significant role during sleep in the maintenance of water and salt during the night (Charloux et al. 1999).

4.4.2 Sleep Enhances Sodium Ions and Water Reabsorption

Sodium ions are required for many physiological processes like bodily water/fluid balance, nerve conduction, cardiovascular functions, muscle contraction, etc. The average sodium concentration in a cell is about 15 mmol, which may vary in different organs (Boundless 2016). It is essential that the sodium concentration should be maintained within the physiological limit. Altered sodium levels are involved in several diseases, for example, patients with acute hyponatremia develop neurologic symptoms such as cerebral edema induced by water movement into the brain, seizures, impaired mental status or coma, and death. Similarly, chronic hyponatremic patients exhibit gastrointestinal tract symptoms such as nausea, vomiting, loss of appetite, some neurologic abnormalities, etc. (Sahay and Sahay 2014). Hypernatremia apart from causing hypertension, brain hemorrhage, and dehydration is also associated with hyperglycemia and mild hypocalcemia (Marcdante et al. 2010). Furthermore, hypertension, caused due to excessive sodium intake, is linked to cognitive deficits (Miller et al. 1968; Grodstein 2007). Therefore, it is imperative that sodium ions should necessarily be maintained at an appropriate concentration in the body.

The homeostatic balance of sodium ions and water is primarily regulated by two hormones: aldosterone and antidiuretic hormone (ADH, also known as vasopressin). As mentioned above, aldosterone increases sodium reabsorption explicitly in the distal convoluted tubule and collecting duct of the nephrons in the kidneys. However, ADH prevents fluid loss and promotes water conservation in the body. The primary stimulus for ADH release from the posterior pituitary gland is an increase in blood osmolarity, which is detected by the osmoreceptors present in the hypothalamus. ADH also stimulates thirst to increase water intake, which lowers blood osmolarity and thus maintaining the electrolytic balance.

Interestingly, it has been observed that the peak amplitude and frequency of release of both aldosterone and ADH occur during sleep. Charloux et al. (1999) have noted that during the regular nighttime sleep periods, the mean aldosterone levels were significantly high during the 11:00 PM to 07:00 AM compared to the 03:00 to 11:00 PM time periods. In the daytime sleep condition, aldosterone levels were higher during the 07:00 AM–03:00 PM compared to wakefulness during the same time periods suggesting that the aldosterone peak is influenced by sleep only rather than circadian timing (Charloux et al. 1999). The release of ADH hormone also increases during the late phase of sleep period (Forsling 2000; Trudel and Bourque 2010). It has been shown that the SCN clock neurons exhibit low neuronal activity during the late phase of sleep. Further, it was found that clock neurons mediate an activity-dependent presynaptic silencing of osmosensory afferent synapses onto ADH neurons. The low firing activity of the SCN's neurons during the late phase of sleep helps obtain the osmoregulatory gain onto ADH neurons. The SCN clock neurons, thus, reversibly modulate the number of functional osmoregulatory synapses and enhance ADH release during the late stage of sleep (Trudel and Bourque 2010).

These studies possibly answer an intriguing question, why we do not feel thirsty while sleeping even for long hours. The underlying reasons could be (a) the high release of aldosterone and (b) ADH hormones during sleep. These two hormones together contribute in water retention in the body. The increased aldosterone level increases renal reabsorption of sodium ions, which in turn elevates osmolality of extracellular fluid. The hypothalamic osmoreceptors sense the changes in osmolality and induce the release of ADH hormone. As a result, water reabsorption from the collecting duct of the kidney is enhanced. The implications of these findings are not limited to obtain the answer of a simple question of not being thirsty during long hours of sleep; it also provides greater insight into how sleep might be involved in rejuvenating almost all the physiological processes.

4.4.3 Sleep Deprivation Alters the Levels of Phosphate Ions in the Body

Phosphate is an intracellular anion predominantly found in several organic moieties and remains bound to lipids, sugars, and proteins molecules. It is involved in several physiological and enzymatic processes in our body. For example, phosphate deficiency leads to tissue hypoxia and cellular dysfunction (Miller and Slovis 2000; Subramanian and Khardori 2000). Alterations in phosphate levels have been implicated in several pathophysiological conditions, such as myalgias, weakness, anorexia, tetany, seizures, coma, rhabdomyolysis, respiratory failure, ventricular tachycardia, etc. (Shiber and Mattu 2002). Besides having several roles in the maintenance of physiological systems, phosphate ions also play an essential role in protein synthesis and its modification and ATP generation.

Studies suggest that sleep also plays a role in the maintenance of cellular homeostatic balance of phosphate ions. It has been found that prolonged sleep deprivation (70–80 h) not only induces changes in the level of some enzymes but also causes hyperphosphatemia (Ilan et al. 1992). Furthermore, phosphate ions are necessarily required for ATP generation, and it has been reported that the surge of ATP production occurs during the initial hours of natural sleep period in wake-active brain areas. The surge is exclusively associated with sleep but not with the time of day. Interestingly, sleep deprivation for 3 or 6 h also altered the generation of ATP (Dworak et al. 2010). These studies suggest that sleep deprivation not only alters the level of phosphate ion but also affects ATP generation.

Parathyroid hormone (1,25-dihydroxy-vitamin D (1,25-(OH)2-D)) plays a vital role in phosphate homeostatic balance through intestinal absorption from the diet and phosphate release from the bone. Chapotot et al. (1996) have studied the 24-h intact parathyroid hormone profile in healthy and sleep-deprived subjects. They found that sleep-wake cycle influences the level of intact parathyroid hormone in blood plasma (Chapotot et al. 1996). The level of mean intact parathyroid hormone levels significantly increased by 13% and mean intact parathyroid hormone pulse

amplitudes by 31% during sleep compared with the corresponding waking hours (Chapotot et al. 1996). Sleep-wake-dependent changes in the level of intact parathyroid hormone in the plasma suggest that sleep could be involved in the modulation of phosphate homeostatic balance.

Hypophosphatemia is considered as one of the reasons for sudden infant death syndrome (SIDS). The cause of SIDS is not yet known, but it is a sudden unexplained death of an apparently healthy baby (<1 year old), which usually occurs during sleep. It has been argued that exposure to a stressful situation, such as maternal separation, can cause enormous loss of phosphate in urine (loss of 50% of the free phosphate pool) within 24 h. The immediate drop of phosphate level also affects the diaphragm contraction, which could be the cause of sudden death (Van Kempen et al. 2013). The timing of death exhibits a temporal relationship between SIDS and sleep. Death of SIDS children usually happens after midnight (between midnight and 6:00 A.M.) (Sullivan and Barlow 2001).

It is very clear from studies that secretion of parathyroid hormone peaks during sleep in healthy subjects and, also, that hypophosphatemia and sleep are both linked with SIDS. It is not known, if (1) SIDS is also associated with an alteration in the sleep-dependent release of parathyroid hormone and/or (2) if high sleep propensity in SIDS causes hypophosphatemia because sleep deprivation induces hyperphosphatemia. Clear answers to these questions require further investigation, but altogether, studies suggest that sleep plays a crucial role in the maintenance of homeostatic balance of phosphate ions as well.

4.4.4 Role of Sleep in the Maintenance of Potassium Homeostasis

Potassium is a necessary ion involved in many physiological processes, such as regulation of acid-base balance, action potential generation, cardiovascular functioning, muscle contraction, etc. The homeostatic balance of potassium ions is also crucial because an alteration in the level of potassium affects the homeostatic balance of other ions (calcium and phosphorous ions are the best examples) (Squire et al. 2013). In addition, the transcellular potassium homeostasis balance depends mainly on acidic/alkaline nature of the medium. Acidosis in transcellular compartments induces cellular efflux of potassium from cells, resulting in hyperkalemia, whereas alkalosis stimulates an influx of potassium, resulting in hypokalemia, without a simultaneous alteration in total body potassium (Mandal 1997).

The role of sleep in the maintenance of potassium homeostatic balance can be understood by considering the changes in the levels of (i) plasma aldosterone and (ii) potassium ions in the plasma itself across sleep and wakefulness. Aldosterone hormone modulates the homeostatic balance of sodium and potassium ions. Aldosterone induces sodium and water reabsorption and potassium ion secretion in the kidney. The increased level of aldosterone reduces plasma potassium level. It has

been found that the level of aldosterone varies across sleep-wakefulness. The level of aldosterone increases during sleep and remains low during wakefulness (Charloux et al. 1999). As a result, the level of potassium should be low during sleep and high during wakefulness. Interestingly, it has been found recently that extracellular potassium levels significantly reduced during sleep and increased during wakefulness (Ding et al. 2016). Ding et al. (2016) have noticed that arousal triggers a rapid rise in extracellular potassium level, while natural sleep or anesthesia induces the opposite changes in extracellular potassium ion concentrations. Nevertheless, it is not precisely known if the reduced level of plasma potassium level during sleep is primarily because of the high level of aldosterone during sleep or its accelerated clearance during sleep by some other factors. It has also been found that the sleep-dependent shift in extracellular potassium ions is fast, compared to other ions (Ding et al. 2016), suggesting that besides the changes in the aldosterone levels across sleep and wakefulness, sleep can also be regulating the homeostatic balance of potassium level in the body.

It has also been reported that potassium ion excretion exhibits diurnal variations, and sleep deprivation alters this variation. The excretion of potassium ions remains elevated during the daytime and reduces during the nighttime. Interestingly, total sleep deprivation for the entire night period induces a significant increase in the potassium ion secretion compared to non-sleep-deprived subjects (Kamperis et al. 2010). Furthermore, it was observed that sleep deprivation did not cause any changes in the level of potassium secretion during the daytime (Kamperis et al. 2010). The increased nocturnal potassium excretion in sleep-deprived subjects suggests that sleep deprivation influences the homeostatic regulation of potassium ions in the body.

4.4.5 Role of Sleep in the Maintenance of Calcium Homeostasis

Calcium is a necessary cation and mineral of bodily electrolytes. It also takes part in the cellular signaling processes as a secondary messenger. Calcium plays an essential role in several physiological processes such as muscle contraction, blood clotting, the release of neurotransmitters from neurons, etc. (Renkema et al. 2008). The concentration of calcium in extracellular fluids is higher than intracellular fluids. In the intracellular compartment, calcium remains stored in cytoplasmic organelles like mitochondrion and endoplasmic reticulum and is released during cellular cell signaling processes (Brini et al. 2013).

There are a few studies suggesting that sleep may play a regulatory role in the maintenance of homeostatic balance of calcium ions in the body. It has been observed that in *Drosophila* brain, the level of calcium ions reduces during sleep and increases during wake conditions in the mushroom body (Bushey et al. 2015). Similar findings have also been reported in the cat (Massimini and Amzica 2001).

The extracellular calcium ion concentration progressively declines in the cortex between the onset and the offset of the depolarizing phase of the oscillatory slow waves during sleep. A significant decline (~20%) of extracellular calcium level occurs specifically during the silence periods of the cortical network during slow-wave sleep, which also significantly affects (~50% decrease) the release of neurotransmitters (Massimini and Amzica 2001).

In mammalian cells, calcium ions remain stored primarily in the endoplasmic reticulum (ER), mitochondria, and Golgi body (Barrige et al. 2003). At the cellular level, it has been found that sleep deprivation induces stress in these cell organelles (Naidoo 2009; Zhang et al. 2014). ER stress causes the changes in the levels of two endoplasmic reticulum (ER) proteins, ER-resident chaperone and immunoglobulin-binding protein (BiP), which are the prime markers of ER stress. It has been found that the level of these two proteins alters with mild sleep deprivation suggesting that sleep deprivation induces cellular stress that activates an adaptive response. The calcium cycle in the ER and mitochondria is also altered when ER remains under stress (Lautenschlaeger et al. 2012). These studies suggest that sleep deprivation may alter calcium cycle/homeostasis.

4.4.6 Role of Sleep in the Maintenance of Iron Homeostasis

Iron is one of the essential elements of life. The formation of red blood cells (RBCs) is highly dependent on iron availability and transportation of oxygen by hemoglobin. Various clinical studies have found that subjects with severe obstructive sleep apnea (OSA) had higher hematocrit levels than subjects with no OSA or mild-to-moderate OSA, which could be because of higher total RBC count to compensate oxygen deficiency (Choi et al. 2006; Feliciano et al. 2017). Further, a significant decrease in hematocrit value and total RBC count has been observed after prolonged (28 h) sleep deprivation (Goodman et al. 1990). Although, the lifespan of RBCs is roughly around 100–120 days, it is surprising that the total count of RBCs drastically reduced within 28 h of total sleep deprivation (Goodman et al. 1990). The acute decrease in total RBC count may be attributed to a phenomenon similar to sports anemia, where RBC is destroyed after running long distances. The presence of free hemoglobin and alteration in iron-binding capacity primarily contributes to sports anemia (Liu et al. 2017). Similarly, it has been reported that iron-binding capacity and plasma iron levels decline after prolonged sleep deprivation (Kuhn et al. 1967). It has also been noticed that 5 days of sleep deprivation markedly reduced the mean level of iron, diminished the absolute and relative amplitude of iron oscillations, disturbed the shape of the daily course of serum iron, and gradually decreased the period of iron rhythm in serum (Kuhn and Brodan 1982). Surprisingly, all these changes were partially restored with sleep recovery (Kuhn and Brodan 1982). These findings clearly demonstrate that inadequate sleep alters iron metabolism as well as visco-elasticity properties of the RBC.

Iron in the brain performs several essential functions such as neuronal myelination, neurotransmitter synthesis, and metabolism. The predominant cell type containing iron in the brain is the oligodendrocyte, which is responsible for the production of myelin. The alteration in the functioning of oligodendrocyte not only causes neuronal hypomyelination but also adversely affects sleep homeostasis and cognition (Beard and Connor 2003; Halassa et al. 2009). Iron also acts as a cofactor for enzymes tryptophan hydroxylase and tyrosine hydroxylase, which are involved in the synthesis of serotonin and dopamine neurotransmitters, respectively (Beard and Connor 2003). Iron deficiency or altered iron metabolism severely affects catecholaminergic neurotransmission in the brain (Beard and Connor 2003), which may in turn effect sleep regulatory systems (Madan and Jha 2012a). Melatonin increases sleep by suppressing the activity of neurons in the brain's circadian clock, and it has been observed that norepinephrine, dopamine, and serotonin influence the synthesis and release of melatonin (Mitchell and Weinshenker 2010). Therefore, imbalance in iron homeostasis or metabolism may affect sleep through both alteration in (a) the functioning of oligodendrocytes and (b) catecholaminergic-mediated synthesis and release of melatonin.

The restless leg syndrome (RLS) patients exhibit poor sleep quality along with low percent iron saturation and serum ferritin level. Interestingly, when these patients were treated with oral iron for 4–5 months, they showed a marked recovery of sleep latency and efficiency with a concomitant reduction in the number of periodic movements (Kryger et al. 2002). An abnormal iron metabolism has been noticed in patients suffering from Parkinson's disease with REM sleep behavior disorder (Hu et al. 2015). The level of transferrin significantly declines in the peripheral system in sleep-deprived subjects (Kuhn et al. 1967). Therefore, it is likely that sleep alteration in Parkinson's patients with REM sleep behavior disorder may cause an increase in the translocation of transferrin from periphery to the brain resulting in altered iron levels.

These studies clearly suggest that sleep deficit may induce homeostatic imbalance of iron in the peripheral as well as central systems. The decreased iron level in the serum and brain alters sleep, possibly by altering the functioning of oligodendrocytes and catecholaminergic-mediated synthesis and release of melatonin. Further, sleep-deprivation-mediated alterations in iron concentration, as well as its metabolism, are restored with sleep recovery, suggesting that sleep may be playing a crucial role in the maintenance of iron homeostatic balance.

4.4.7 Role of Sleep in the Maintenance of Magnesium Homeostasis

Magnesium is another most abundant mineral in our body. Half of the body's magnesium is found in the bones and the other half in cells of the remaining body organs. Many biological systems such as the muscle, nerve, heart's steady

rhythmicity, immune system, and bones essentially require magnesium for their proper functioning. Magnesium is considered to be a natural agonist and antagonist of GABA and NMDA receptors (Abbasi et al. 2012). Interestingly, it has been observed that it plays a critical role in sleep regulation as well. Murck and Steiger have found that oral administration of magnesium significantly increases the sleep EEG power within the spindle frequency range (11.0–12.9 Hz), but does not change SWS delta power throughout the night (Murck and Steiger 1998). Later, Held et al. have reported that oral administration of magnesium significantly increased slow-wave sleep as well as EEG delta and sigma power in elderly subjects (Held et al. 2002). In elderly subjects, magnesium supplement appears to improve insomnia and early morning awakening and serum melatonin concentration (Abbasi et al. 2012). Besides these, magnesium therapy has also been proposed for the treatment of periodic leg movements-related insomnia. Magnesium was orally administered to subjects suffering from insomnia related to periodic leg movements and mild-to-moderate RLS. The drug was administered in the evening over a period of 4–6 weeks. It was found that following magnesium treatment, periodic leg movement syndrome-mediated arousals decreased, and sleep efficiency improved significantly (Hornyak et al. 1998).

Sleep, on the other hand, also plays an essential role in the maintenance of magnesium level in the body. It has been found that sleep deprivation decreases mean erythrocyte magnesium concentration and intracellular magnesium level (Tanabe et al. 1997; Takase et al. 2004). Magnesium is an essential cofactor for many enzymatic reactions, especially those that are involved in energy metabolism and neurotransmitter synthesis (Morris 1992). Magnesium is very closely linked to electrolytic balance. The concentration of various other minerals like calcium and phosphate fluctuates with alterations in magnesium levels (Renkema et al. 2008). Sleep has a profound role in maintaining optimal levels of magnesium by influencing the regular pulses of aldosterone hormone in the plasma (Charloux et al. 1999; Hurwitz et al. 2004), which is responsible for regulating magnesium metabolism (Swaminathan 2003).

Elevated magnesium level in the brain upregulates NMDAR signaling and concomitantly prevents synaptic loss and memory deficit in aged rat models (Slutsky et al. 2004, 2010). Magnesium plays a crucial role in the glutamate-dependent induction of long-term potentiation (LTP) in the neurons. Prolonged membrane depolarization helps remove magnesium from glutamatergic NMDA receptors. Removal of magnesium from NMDA receptors allows calcium influx, which in turn triggers the second messenger systems to activate kinases, gene transcription, and protein synthesis (Rajadhyaksha et al. 1999; Bauer et al. 2002). The elevation of brain magnesium enhances learning and memory in young and aged rats (Slutsky et al. 2010). This elevation of brain magnesium also increases the activity of NR2B subunits of NMDAR, NMDAR signaling, and synaptic plasticity with a concomitant increase in number of presynaptic buttons in the hippocampus, which is the primary area of the brain responsible for learning and temporarily storing new information (Slutsky et al. 2010). The NMDAR-dependent induction of LTP in the hippocampus and increased synaptic efficacy after learning essentially require sleep (Madan and

Jha 2014). It is not known, however, if magnesium plays a role in the sleep-dependent induction of LTP and synaptic efficacy. Nonetheless, the level of magnesium ion changes across sleep-wake states (Ding et al. 2016). The level of free magnesium ions exhibits minor but consistent shift, with decreasing level during sleep to wake and increasing level from wake to sleep transitions in the cortical brain areas (Ding et al. 2016). Such consistent changes in the level of magnesium ions have also been observed under anesthetized conditions.

These findings suggest that (a) the homeostatic extracellular ionic regulation may be involved in the alteration of behavioral states and/or (b) changes in the ionostatic level across different behavioral states may facilitate different neuromodulators in exerting consistent and optimal changes in neuronal functions and synaptic efficacy. The implications of this phenomenon, as has been proposed, would be that this "ionostatic control" of neural activity might provide a backdrop for coordinating shifts in the behavioral state through the extensive regulation of excitability without relying on complicated receptor activation in diverse subclasses of neurons (Ding et al. 2016).

4.4.8 Role of Sleep in the Maintenance of Zinc Homeostasis

Few studies have indicated that the suboptimal level of zinc in the blood and/or brain may cause impairment in intrinsic sleep regulation and sleep quality. The subjects having an optimal zinc level and/or optimal zinc-copper ratio in the serum experienced longer sleep duration compared to the subjects having suboptimal or altered ratio (Song et al. 2012). On the other hand, subjects having a regular sleep (7–9 h per night) had the highest concentration of serum zinc compared to short (<7 h) and long (>9 h) sleepers (Zhang et al. 2009). The cross-sectional and longitudinal association between zinc status and sleep outcomes in normal school-goers has also been investigated. In a cross-sectional analysis, a significant link between zinc concentration and sleep quality in adolescence has been observed. It was found that adolescents having higher blood zinc concentrations experienced usual sleep quality (Ji and Liu 2015). Therefore, it was suggested that the likelihood of sleep disturbances in adolescents could be minimized with the increasing concentration of zinc. Surprisingly, no link was found between blood zinc level and sleep outcomes at preschool age (Ji and Liu 2015). It was, however, proposed that the lower concentrations of zinc in blood at the preschool age may be a predictor of an increased likelihood of poor sleep quality and sleep efficiency at the adolescence age (Ji and Liu 2015). Thus, it seems that the optimal level of zinc in the blood could be associated with better sleep quality.

Zinc supplementation can also improve sleep. The sleep amount in children suffering from iron deficiency anemia significantly increased with 12-month iron and zinc supplementation (Kordas et al. 2009). Not only children suffering from iron deficiency anemia but also all healthy subjects exhibited a remarkable increase in sleep amount with 60 days of triple supplementation, a combination of melatonin,

magnesium, and zinc taken before bedtime (Rondanelli et al. 2011). The indispensable effects of natural sources enriched with zinc ions, such as oysters and yeast extracts, have also been investigated. It was found that individuals treated with daily zinc supplements from natural resources for 3 months had improved sleep latency and sleep efficiency compared to control subjects (Saito et al. 2017). How zinc promotes sleep is precisely not known, but Zn remains stored and co-released from glutamatergic and glycinergic axonal terminals in the brain (Danscher and Stoltenberg 2005). Few sleep-active or sleep-promoting neurons are glycinergic in nature (Anaclet et al. 2012). Hence, it is likely that Zn may activate the glycinergic sleep-promoting neurons, which in turn may enhance sleep.

The role of sleep in the maintenance of zinc homeostasis is not known. However, psychological stress and depression reduce the level of zinc in the brain particularly in the hippocampus (Dou et al. 2014). Under normal conditions, zinc has very low permeability across the blood-brain barrier. Zinc concentration in the brain remains exceptionally stable regardless the serum concentration (Blair-West et al. 1990). Nonetheless, rapid exchange of zinc between the blood and brain takes place during the first 30 min following intravenous administration under certain situations (Pullen et al. 1990). It is also known that several stress paradigms induce a significant reduction in zinc concentration as well as alteration in the blood-brain barrier (Cieslik et al. 2011). Similarly, chronic sleep deprivation condition alters the blood-brain barrier and increases the permeability of several ions (Sharma et al. 2015). It is likely that the permeability of zinc across the blood-brain barrier increases under chronic sleep-deprived conditions, which can restore sleep as well as sleep-loss-mediated alteration in the neuronal circuitries (Cieslik et al. 2011).

4.5 Sleep and Energy Homeostasis: Regulation of Glucose Metabolism

Several papers have indicated that glucose utilization reduces during sleep. For example, plasma glucose level significantly declines after 8 h fasting while being awake, but it remains relatively constant and stable during sleep, which is also akin to fasting state (usually no food intake happens when asleep) (Simon et al. 1998). In one of the exciting studies, a link between sleep and glucose regulation was investigated. Glucose was infused continuously during sleep. This inhibits endogenous glucose production, and then the observed plasma glucose level was interpreted as changes in glucose utilization. It was observed that the levels of glucose increased during the early part of nocturnal sleep by approx. 20%, which returned to the basal level only by morning (Scheen et al. 1996). Further, these authors have noticed that with constant glucose infusion overnight, glucose level increased during NREM sleep, while it was reasonably stable during REM sleep (Scheen et al. 1996). In healthy subjects, whole-brain glucose metabolism significantly decreases during NREM sleep, and it could be one of the reasons for increased glucose levels during

NREM sleep (Nofzinger et al. 2002). In addition, it has been proposed that reduction of peripheral glucose utilization may be another cause of increased glucose level during NREM sleep (Maquet et al. 1990; Boyle et al. 1994). The propensity of REM sleep, which is an energy-consuming state, increases during the early morning. Hence, it was argued that the enhanced glucose level during sleep would fall back to the basal level during the early morning. Interestingly, the glucose level decreases during daytime sleep as well (Van Cauter et al. 1991), suggesting a modulatory role of sleep in the regulation of glucose level unrelated to the time of day.

Sleep deficit also alters glucose level profoundly. After a constant glucose infusion in non-sleep-deprived and sleep-deprived subjects, it was observed that in total sleep-deprived subjects, plasma glucose levels increased much less during the first half of the night than those getting regular sleep (Knutson 2007). During the second half of the night, glucose levels decreased under both conditions, but the decline was significantly different in sleep-deprived and non-sleep-deprived subjects (Knutson 2007). Furthermore, it was also found in that study that after sleep deprivation, plasma glucose levels were high in the midmorning to late afternoon despite similar insulin levels (Knutson 2007). Postprandial blood glucose level increases significantly in subjects suffering from chronic sleep loss as compared to subjects having normal sleep even though the insulin levels remain the same in both groups. These studies suggest that chronic or acute sleep deficit may induce some pathophysiological conditions, which may contribute to the development of glucose intolerance or diabetes.

In addition, glucose may induce sleep by exciting the sleep-promoting neurons, primarily located in the ventrolateral preoptic area (VLPO) (Saper et al. 2010). These neurons play an essential role in the induction and maintenance of NREM sleep. A rise in extracellular glucose concentration in the VLPO activates these sleep-promoting neurons as well as NREM sleep (Varin et al. 2015). It was proposed that glucose-induced neuronal excitation causes the closure of ATP-sensitive potassium (KATP) channels. Hence, the extracellular glucose can monitor the gating of KATP channels of sleep-promoting neurons, which may help the sleep-promoting VLPO neurons to change their excitability depending on the extracellular energy status. All these studies suggest that sleep and glucose homeostatic regulatory machineries are intimately linked, and an alteration in either of the two systems has a profound impact on physiology and health.

4.6 Sleep Helps in Toxin Clearance from the Body

Sleep performs several restorative functions, and one among them is a clearance of toxins or toxic metabolites. The role of sleep in metabolite clearance can be assessed primarily through two different approaches: (a) the influence of metabolites on behavioral states and (b) the production of different metabolites across different behavioral states. Some metabolites strongly influence sleep-wake states. For example, mild hypercapnia induces sleep, while strong hypercapnia induces wake state

(Fraigne et al. 2008). Supplementing 2% CO_2 in breathing air significantly increased sleep by increasing NREM sleep time and decreased sleep latency (Fraigne et al. 2008). Sleep parameters deteriorated with an inspired CO_2 of 6%. Addition of 4% CO_2 in the inspired air, however, did not produce any significant change in sleep duration. Interestingly, the breathing rate remains higher in NREM and REM sleep under mild hypercapnia compared to the normocapnia. The increased breathing rate after mild hypercapnia during sleep may help in removing excess CO_2 from the body. In addition, the breathing rate remains low during NREM sleep and increases during REM sleep under normal conditions. It is likely that REM sleep might act as a sentinel to help in maintaining the CO_2 level within physiological limits (Madan and Jha 2012a).

Neurons are highly sensitive to their environment, and changes in ionic composition in and around neurons affect their functionality. Therefore, metabolites need to be cleared intermittently from the interstitial space. The periodic clearance of these metabolites can be facilitated if the dimension of interstitial space increases from time to time. The volume of cortical interstitial space increases interestingly by more than 60% during sleep (Xie et al. 2013). Using real-time assessments of the influx of CSF tracer (Texas red-dextran, 3 kD) in awake and sleeping mice, it was noticed that periarterial and parenchymal tracer influx was reduced by ~95% in awake as compared with sleeping mice (Xie et al. 2013). Further, a radiolabeled amyloid beta protein (125I-Aβ1-40) was injected intracortically in naturally awake and sleeping mice. Brains of these animals were harvested 240 min later to analyze the retention of 125I-Aβ1-40. It was found that the clearance of exogenously applied Aβ1-40 was twofold faster in the sleeping mice as compared to the wake mice (Xie et al. 2013). The study suggests that sleep facilitates the clearance of degradation products of neural activity that accumulate during wakefulness.

A link between sleep loss with the accumulation of CSF Aβ42 in a normal aging group has also been observed. It is well known that brain's amyloid beta protein is an outcome of neuronal activity, and its level in the brain peaks during wake and falls during sleep (Beekly et al. 2007). NREM sleep duration correlates with CSF Aβ42 levels in aged subjects. Varga et al. (2016) have found a significant inverse correlation between CSF Aβ42 and NREM sleep duration and between % NREM sleep and slow-wave activity. CSF Aβ42 was not correlated with the duration of REM sleep (Varga et al. 2016). These findings demonstrate that the brain may not be in an optimal functional state during sleep deprivation to facilitate the clearance of metabolites.

Sleep possibly facilitates the clearance of biomolecules between the cerebrospinal fluid (CSF) and interstitial fluid (ISF) through convective flow to remove toxic metabolites from the brain. It was proposed that the glymphatic system is strongly stimulated by sleep, which is associated with an increase in interstitial volume (Mendelsohn and Larrick 2013). The increase in interstitial volume possibly takes place by shrinkage of astroglial cells. It is possible that sleep has a role in shrinkage of glial cells. Sleep deprivation may induce glymphatic dysfunction, which may, in turn, be involved in the pathogenesis of neurodegenerative diseases (Mendelsohn and Larrick 2013).

4.7 The Implication of Homeostatic Ionic Imbalances in Cognitive Dysfunctions

Optimal neuronal function is the outcome of their environment milieu. Therefore, any abrupt change may cause neuronal dysfunction, which may lead to pathophysiological conditions. For example, depletion of magnesium in the hippocampus seems to be a crucial pathogenic factor in the progression of Alzheimer's disease (Durlach 1990). Similarly, alteration in the mitochondrial calcium uniporter during development causes memory impairment without altering the capacity to learn. Alteration in uniporter activity during development impaired adult memory, but similar inhibition during adulthood did not affect memory (Drago and Davis 2016). Additionally, changes in the level of potassium, sodium, iron, glucose, and other ions in either the CSF or ISF profoundly induced learning deficit (Williams 2001; Hoyer 2003; Ozawa et al. 2012)

Changes in ionic concentration may induce an alkalosis or acidosis condition, which has a profound effect on cognitive ability. Alkalosis causes brain vasoconstriction, which in turn affects the processing capability of the brain and probably diminishes cognition (Farnam 2014). Antidiuretic hormone plays an essential role in the maintenance of electrolytic balances. In one of the exciting experiments, ADH injection into non-preloaded normal rats (which presumably had regular water and electrolyte balance) has no significant aversive or rewarding effect in T-maze learning experiments. However, the preloaded animals (which had an excess of either H_2O or NaCl) were motivated to learn. The H_2O-loaded animals chose the side where they could avoid the ADH microinjection, whereas the NaCl-loaded group prefers the side where they can receive ADH injection so that they can restore normal water level rapidly. The results show that ionic imbalances induce visceral learning which is mediated through the central nervous system and helps in maintaining ionic homeostasis (Miller et al. 1968).

Cellular pH or the level of hydrogen ion concentration in the body may also influence learning or cognitive ability. Elevated CO_2 levels in animals cause intense fear and panic disorder (Papp et al. 1993). In a healthy human, CO_2 produces dose-related increases in anxiety, but in patients of panic disorder, the increase in anxiety and somatic symptoms induced by 5% CO_2 exceeded those in healthy subjects (Woods et al. 1988). In the brain, H^+ can be rapidly generated by CO_2 and water, which is catalyzed by an enzyme *carbonic anhydrase*, and this proton ion causes central acidosis. It has been proposed that perhaps acidosis triggers central proton-gated currents and potentiates the feelings of panic (Wemmie et al. 2004). CO_2 also enhances the contextual fear memory retention in mice by activating acid-sensing ion channels (ASIC) (Wemmie et al. 2004). Overexpressing human ASIC1a by using the pan-neuronal synapsin-1 promoter, it has been found that transgenic overexpression of ASIC1a significantly increased neuronal acid-evoked cation currents in the amygdalar neurons. Further, they found that overexpressing ASIC1a in the amygdala enhanced fear memory (Wemmie et al. 2004).

Hydrogen ions can also act as a potential neurotransmitter (Du et al. 2014). It has been found that stimulating the presynaptic terminals increases proton concentration in synapses. Potential receptors for these presynaptically released protons are acid-sensing ion channels, Na^+-, and Ca^{2+}-permeable channels that are activated by extracellular acidosis. Interestingly, the proton-activated ASICs generate excitatory postsynaptic currents in the amygdala pyramidal neurons, and both protons and ASICs play an essential role in the induction of synaptic plasticity in lateral amygdala neurons. In fact, it is argued that based on these functions, protons are indeed neurotransmitters, which act through the postsynaptic ASICs receptor. Du et al. have established that protons (neurotransmitter) and ASICs (proton receptor) are critical for amygdala-dependent learning and memory (Du et al. 2014). The drop in pH by H+ released from neuronal vesicles in synaptic cleft enhanced the LTP in amygdalar neurons. Further, increasing the buffering capacity of the solution decreased LTP induction suggesting that drop in pH is indeed necessary for memory formation, at least in case of emotional memories (Wemmie et al. 2004; Du et al. 2014). These studies imply that proton ions can act as neurotransmitters, and this could well become an emerging field with respect to studying its functions and involvement in treating cognitive disorders.

In one recent study, it has been found that the pattern of breathing creates differential electrical activity in the human brain, which may be involved in emotional judgments and memory recall (Zelano et al. 2016). They have found that the memory recall of a fearful face was quicker during inhalation than during exhalation and suggest that the breathing phase systematically influences cognitive tasks related to the amygdala and hippocampal function. It has also been reported that learning-dependent changes in pH occur in the brain, and pH-sensitive acid-sensing ion channels are activated due to a fall in pH, which further starts a signaling cascade in neurons necessary for memory acquisition (Ziemann et al. 2009). Moreover, besides the role of CO_2 in REM sleep initiation (REM sleep helps in elimination of excess CO_2 built up during NREM sleep and ensures the acid-base balance by elevating the breathing rate), it may also help in fear memory consolidation (Popa et al. 2010; Du et al. 2014). Therefore, REM sleep could act as a bridge between the acid-base balance during sleep and memory consolidation processes. Any change in either REM sleep or acid-base homeostasis could potentially impair cognition.

4.8 Conclusions

There is definite evidence suggesting that chemoregulation and sleep are two independent systems but closely linked. Sleep disturbances either qualitatively or quantitatively alter ionic balances in the brain and body. The manifestation of different breathing rates during NREM and REM sleep and ionic imbalances in the body fluids in various sleep-related pathophysiological disorders like OSA suggest that sleep may be playing a vital role in balancing the physiological acid-base status. Endocrine system plays a central role in ionic homeostasis, and

interestingly the activity of some endocrine axis shows sleep-dependent rhythmicity. The level of some cations such as potassium, calcium, sodium, or magnesium in the brain alters during sleep and wake conditions (Ding et al. 2016). On the other hand, deficiency of these ions not only alters some vital physiological functions but also induces a significant sleep deficit. For example, magnesium deficiency in the elderly population has been shown to be the primary cause of insomnia, and oral supplementation improves sleep in such individuals (Abbasi et al. 2012). Magnesium supplementation improves insulin sensitivity in type 2 diabetic patients and also their sleep efficiency (Rodriguez-Moran and Guerrero-Romero 2003).

Neurons can only be optimally functional if their environmental milieu is adequately maintained or else it may lead to the progression of pathophysiological conditions. For example, depletion of magnesium in the hippocampus seems to be involved in the progression of Alzheimer's disease (Durlach 1990). Similarly, alteration in the mitochondrial calcium uniporter causes memory impairment. In this chapter, we have proposed that sleep plays an essential role in the maintenance of optimal acid-base balance. The influence of acute and chronic sleep loss on ionic inconsistency, however, is not known. In addition, a detail mechanism of sleep-loss-mediated alteration in acid-base dysregulation is not known. It would be intriguing to know how the ionic imbalances cause insomnia as well as cognitive deficits. Future studies may provide more insight into a close link between disruptive sleep, impaired cognition ability, and acid-base imbalances.

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Chapter 5
Sleep and Brain Plasticity

Marcos G. Frank

Abstract Recent studies combining sleep measurements with measurements of neuronal plasticity have provided important insights into how sleep influences synaptic remodeling in the central nervous system. Scientists have employed different approaches to this problem that include classic models of plasticity in vivo and in vitro and more theoretical organizing principles. The resulting findings have in turn led to a reassessment of theories of sleep function and the role of sleep in brain plasticity. In this chapter, I discuss these key findings and current theories that posit different roles for sleep in neuronal plasticity.

Keywords Synapse · Remodeling · Function · Circadian · Maturation · Sleep

5.1 Introduction

The function of sleep is unknown, but there is a growing scientific consensus that it plays a role in brain plasticity. This is in part because of its historical and enduring association with processes that require brain plasticity, such as learning, memory, and neurodevelopment. Scientists have now begun to uncover the network, cellular, and molecular events that occur in sleep that may explain the effects of sleep on these latter processes. More specifically, scientists are using what is known about the cellular and molecular mechanisms of synaptic plasticity to find links between the electrophysiological, chemical, and molecular activity during sleep with modulation of synaptic connections in the brain. The establishment of such links holds the greatest promise for solving the enduring mystery of sleep function.

In this chapter, I summarize key evidence that supports a role for sleep in brain plasticity and provides insight into the underlying mechanisms. This includes indirect evidence, which comes from studies of how sleep influences perception,

M. G. Frank (✉)
Elson S. Floyd College of Medicine, Washington State University Spokane, Spokane, WA, USA
e-mail: marcos.frank@wsu.edu

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learning, and memory, and direct evidence, which are physical measures of synapse number or strength before and after sleep. These can be further divided into what I call "top-down" and "bottom-up" approaches. "Top-down" approaches have at their heart an organizing principle or theory that attempts to explain the role of sleep in plasticity in a comprehensive way. "Bottom-up" approaches instead ask more basic, simpler questions about how sleep or sleep loss impacts classic models of plasticity in vivo or in vitro. The results of the latter investigations do not require that any particular "top-down" theory be true. However, any "top-down" theory must account for "bottom-up" results. Ideally, both approaches should converge and thus reveal exactly how sleep does (or does not) influence brain plasticity.

5.2 Bottom-Up Approaches to Sleep-Dependent Plasticity: The Visual Cortex and Hippocampus

5.2.1 Sleep and Plasticity in the Visual Cortex: Ocular Dominance Plasticity (ODP) and Orientation-Stimulus Response Plasticity (OSRP)

ODP refers to electrophysiological and morphological changes in visual cortical neurons in vivo triggered by monocular deprivation (MD) or other changes in patterned vision (Wiesel and Hubel 1963; Hubel and Wiesel 1970). ODP is more easily induced during a critical period of development, and it commonly shares several mechanisms that mediate Hebbian and non-Hebbian plasticity in the adult hippocampus and non-sensory cortex. The induction of ODP is considered *physiological* for the following reasons: (1) It develops in an intact unanesthetized brain in response to the alterations in the visual inputs that animals actually experience. (2) Although ODP is induced artificially using the MD protocol in the laboratory, this change in visual input occurs naturally in amblyopia. Amblyopia is caused when patterned vision is altered in one eye during early life or when the two eyes fail to converge. It occurs in humans and other mammals with binocular vision. The induced plasticity in response to altered vision involves naturally occurring changes in synaptic proteins and molecules as a part of an *adaptive* response. (3) The underlying plasticity is present, with or without MD, as it governs cortical adjustments to visual input that normally occur during the critical period. These adjustments are thought essential for the development of binocular vision, acuity, and other visual response properties in cortical neurons (for review see Spolidoro et al. 2008; Tropea et al. 2009; Smith et al. 2009; Espinosa and Stryker 2012).

In the cat, during the peak of the critical period, merely 6 h of sleep significantly increases the effects of MD on cortical neurons, and the same process does not occur if animals are sleep-deprived (Frank et al. 2001). The precise mechanisms governing this process are not entirely known, but they are similar to those that mediate Hebbian long-term potentiation (LTP). For example, both acute (Aton et al. 2009)

and chronic recordings (Aton et al. 2012) of single neurons show that responses to the non-deprived eye become stronger after sleep. In comparison, sleep does not influence the magnitude of depression seen in the deprived eye pathway. This process is activity-dependent (Jha et al. 2005), and inhibiting the N-methyl-D-aspartate receptor (NMDAR), the protein kinase A (PKA), the extracellular-regulated kinase (ERK), or the mammalian target of rapamycin (mTOR) during post-MD sleep inhibits this potentiated response (Aton et al. 2009; Seibt et al. 2012). In addition, post-MD sleep is accompanied by activation of several kinases associated with the induction of LTP and phosphorylation of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) that lead to trafficking and insertion of this receptor into the postsynaptic membrane (Aton et al. 2009). Post-MD sleep also promotes the synthesis or phosphorylation of several proteins implicated in LTP (Seibt et al. 2012; Dumoulin et al. 2015).

An interesting observation in the cat is that induced plasticity during wake and sleep appears to be governed by distinct mechanisms. In addition to a difference in the direction of plastic change (weakening in wakefulness, strengthening in sleep), the MD-mediated induction of plasticity in the awake brain does not require protein synthesis. In contrast to sleep-dependent plasticity, intracortical blockade of mTOR or ERK (which also activates mRNA translation) has no effect on circuit weakening in wakefulness. In addition, several plasticity-related mRNAs are upregulated by visual experience, but the translational process does not begin until sleep occurs (Seibt et al. 2012). This suggests that the translation and transcription of mRNAs related to plasticity are divided across sleep and wakefulness.

A two-stage process in ODP is further shown by a recent study of single-neuron activity in freely behaving animals. Aton et al. (2013) used chronic, stereotrode recording to track the single neuronal activity and interactions of visual cortical cells before, during, and after a period of MD. In contrast to earlier studies employing similar longitudinal recording (Mioche and Singer 1989), the activity of neurons was also recorded across sleep-wakefulness. In the awake animal, MD caused a significant decrease in the firing rate of fast-spiking neurons (i.e., putative GABAergic cells) in the visual cortex. This decrease in neuronal activity persisted during the first 6 h of post-MD sleep accompanied by an increase in firing in regular spiking (i.e., putative excitatory neurons). The decrease in fast-spiking activity was also proportional to plastic changes in regular spiking neurons observed after sleep. This suggests that in addition to changes in the deprived eye pathway, MD alters intracortical inhibition which contributes to sleep-dependent changes in excitatory circuits.

These effects in vivo are unlikely explained by indirect effects of the experimental procedures (for discussion see Frank and Cantera 2014). ODP is remarkably resistant to the effects of the stress hormone corticosterone (Daw et al. 1991), and corticosterone levels in these experiments are tenfold lower than those reported to reduce ODP (Dumoulin Bridi et al. 2015). Short-term MD used in these studies also did not significantly reduce non(N)-rapid-eye-movement (REM) slow-wave activity (SWA) or alter basic visual processing in cortical neurons, except the expected loss of response to the deprived eye. Visual responses were completely normal in the

intact visual pathway, which was expected if the underlying processes are physiological.

OSRP is a form of in vivo LTP also induced by changes in visual input but present in the developing and adult visual cortex. In mice, brief exposure to a visual stimulus (phase-reversing, oriented gratings) results in enhanced cortical (V1) responses to stimuli of the same orientation (Frenkel et al. 2006). OSRP is considered an in vivo form of LTP of cortical glutamatergic synapses because it requires the same cellular mechanisms as LTP in vitro (Frenkel et al. 2006) and occludes tetany-induced thalamocortical LTP (Cooke and Bear 2010). Interestingly, OSRP is not present immediately after training in an awake mouse. It is only observed after a subsequent period of sleep and suppressed by sleep deprivation (Aton et al. 2014). A follow-up investigation (Durkin and Aton 2015) showed that these changes could not be explained as a form of synaptic weakening, as recently suggested (Cirelli and Tononi 2015). Therefore, although the underlying mechanisms during sleep governing this process are presently unknown, they most likely involve those implicated in classic LTP.

5.2.2 Sleep, Memory, and Hebbian Plasticity

The role of sleep in brain plasticity has traditionally been investigated using classic forms of hippocampal-dependent learning and tetany-based forms of Hebbian LTP and long-term depression (LTD). The more direct tests include the effects of sleep and sleep deprivation on various forms of learning or the ability to induce LTP and LTD. Overall, sleep deprivation appears to interfere with hippocampal-dependent learning and memory consolidation in rodents (Pearlman 1981; Block et al. 1981; Smith 1985, 1995). These include tasks such as contextual fear conditioning, novel or spatial object recognition, and the Morris water maze. On all of these tasks, there is a window of time after experience where sleep deprivation impairs memory formation. The timing of this window varies considerably across studies and may be task, species, and strain dependent (reviewed in Benington and Frank 2003). The early studies of the 1970s and 1980s were often criticized because sleep deprivation is a stressor and stress hormones can independently influence hippocampal function and plasticity. However, in the last 20 years, scientists have continued to find a sleep deprivation effect even in cases where stress is not a factor (reviewed in Frank and Benington 2006). Therefore it appears that after the experience, sleep activates secondary plasticity processes that consolidate certain forms of memory. These appear to involve protein synthesis, as the translational machinery in the hippocampus is suppressed during sleep deprivation but recovers with subsequent sleep (Havekes and Abel 2017).

Consistent with the activation of plasticity mechanisms in sleep, hippocampal LTP can be induced during REM sleep, whereas similar stimulus protocols during non(N)REM sleep have inconsistent effects or produce LTD (reviewed in (Benington and Frank 2003; Hennevin et al. 2007). Sleep deprivation also affects

the induction or maintenance of LTP in vivo and in vitro. For example, sleep deprivation impairs hippocampal LTP in anesthetized and awake rodents process in the medial prefrontal cortex (Romcy-Pereira and Pavlides 2004; Marks and Wayner 2005; Kim et al. 2005). Several studies also show that in vitro hippocampal LTP (either the induction or maintenance) is reduced in rodents that undergo varying amounts of REM sleep deprivation, total sleep deprivation, or sleep restriction prior to sacrifice (Kopp et al. 2006; Arrigoni et al. 2009; Campbell et al. 2002; Davis et al. 2003; Ishikawa et al. 2006; McDermott et al. 2003, 2006; Ravassard et al. 2006, 2009; Tartar et al. 2006; Florian et al. 2011; Vecsey et al. 2009; Chen et al. 2006). Interestingly, when REM sleep is restored (after prior deprivation) or increased in rodents, this reverses deficits in hippocampal LTP (Ravassard et al. 2009, 2015).

The underlying mechanisms mediating the effects of sleep loss on LTP and LTD are not completely understood. It appears that the effect may not be simply due to indirect effects of the sleep deprivation procedures. For example, these deficits can be dissociated from changes in stress hormones (Kopp et al. 2006; Ravassard et al. 2009, 2015). Reduced plasticity may instead be associated with a decline in hippocampal NMDA receptor function (Kopp et al. 2006; Chen et al. 2006; McDermott et al. 2005; Longordo et al. 2009) and ERK/MAPK activation (Ravassard et al. 2009) combined with reductions in hippocampal dendritic spines (Havekes et al. 2016), plasticity-related mRNAs or proteins (Ravassard et al. 2015; Guzman-Marin et al. 2006; Davis et al. 2006), and elevated concentrations of PDE4 (Vecsey et al. 2009) and extracellular adenosine (Arrigoni et al. 2009; Florian et al. 2011).

5.3 Top-Down Theories of Sleep-Dependent Plasticity: The Hippocampal-Neocortical Dialogue (HND) and the Synaptic Homeostasis Hypothesis (SHY)

5.3.1 The HND

In the late 1990s, Gyuri Buzsaki proposed that during sleep memories were transferred from the hippocampus to the neocortex. He called this process the "hippocampal-neocortical dialogue" (HND) and hypothesized that it explained how sleep consolidates memory. The HND theory was based in part on theoretical considerations concerning how information flow in and out of the hippocampus could be modulated by different concentrations of neuromodulators (Buzsaki 1996). According to the HND, during sleep, the hippocampus enters a "closed-loop" state of activity, dominated by oscillatory bursts (sharp waves or ripples) that communicate a waking memory trace to neocortical targets. The periodic barrages of inputs to the neocortex then potentiate cortical synapses. Key predictions of the HND are that these oscillatory events carry information about what the animal experienced and that a flow of information occurs during sleep. In the original formulation of HND, the critical sleep state for this communication was NREM sleep.

The first prediction has largely been borne out. Following early suggestive findings from Winson and Pavlides (Pavlides and Winson 1989), some studies from the McNaughton laboratory demonstrated that correlational patterns in firing that matched the order in which cells fired during maze running "replayed" during NREM sleep (Wilson and McNaughton 1994; Skaggs and McNaughton 1996). Subsequent studies report variants of replay in the rodent hippocampus, ventral striatum, and cortex (Wilson and McNaughton 1994; Skaggs and McNaughton 1996; Lee and Wilson 2002; Louie and Wilson 2001; Kudrimoti et al. 1999; Pennartz et al. 2004; Ji and Wilson 2007; Yang et al. 2014). Forms of replay (or reactivation) have also been found in an impressive number of animal species, ranging from birds (Dave and Margoliash 2000) and cats (Dumoulin Bridi et al. 2015) to primates (Hoffman and McNaughton 2002), and, based on brain imaging, possibly humans (Maquet et al. 2000; Peigneux et al. 2004; Deuker et al. 2013).

With respect to the second prediction, the situation is not as clear, but supporting evidence has been steadily accumulating over the last 10 years. There are interesting correlations between ripples and sharp waves and thalamocortical spindles and cortical slow waves consistent with this hypothesis (Siapas and Wilson 1998; Battaglia et al. 2004; Sirota et al. 2003). In addition, though quite rare, there are instances when hippocampal and cortical replays occur simultaneously (Ji and Wilson 2007; Qin et al. 1997; Wierzynski et al. 2009). The dialogue between the neocortex and hippocampus also appears to be multidirectional, as thalamic or cortical activity can precede and even predict hippocampal activity during sharp-wave ripples (Rothschild et al. 2016; Diekelmann and Born 2010). Computational models also show that precisely timed hippocampal ripples and cortical up and down states can lead to persistent changes in cortical synaptic weights (Wei et al. 2016).

5.3.1.1 Reexamining the HND

The HND provides a very attractive theory for sleep-dependent plasticity. Nevertheless, there are several areas that require further investigation. First, hippocampal replay is not unique to sleep. It can be observed during periods of waking immobility and even during intense exploration (Kudrimoti et al. 1999; O'Neill et al. 2006; Foster and Wilson 2006). It is possible that replay in sleep could be qualitatively different than wake; it is, however, yet to be determined. Therefore, sleep may be sufficient, but not necessary for the induction of replay. Second, replay in sleep is commonly not observed at the time of learning. It is mostly observed after the animal learns the task. In most studies, animals have been pretrained for several days to weeks on a maze before replay was detected (Peyrache et al. 2009; Frank 2007). The appearance of replay after several training trials might reflect a gradual progression of engram that appears after initial learning and contributes in memory transfer from short-term stores (hippocampus) to long-term stores (neocortex). However, it is likely that replay could be a decreasing reverberation of a well-ingrained pattern of neural activity present during wakefulness. This may explain why replay exhibits an ephemeral nature. It is usually observed within the first 20–30 min of NREM sleep

and then diminishes. In some measures, it also accounts for only a fraction of the total variance in neuronal activity (reviewed in Frank 2007).

Very little is known about the effects of novel learning on neuronal replay, which might distinguish between these two possibilities. Some reports suggest that neuronal replay associated with novel experience appears during sleep; however, the novel tasks are often very similar to familiar tasks. For example, one study has reported substantial overlap (between 70% and 77%) in neuronal activity in the familiar versus novel maze tasks (Kudrimoti et al. 1999). Some other studies have although reported novelty-induced neuronal replay in the sleeping rat forebrain (Ribeiro 2004; Ribeiro 2007), but this has been challenged on technical and methodological grounds (Tatsuno et al. 2006).

More recent findings indicate that neuronal replay may occur following novel experience. In one study, rats were trained for novel learning task. Recording of neuronal ensemble from the medial prefrontal cortex of these rats showed that neuronal activity patterns induced by learning were also "replayed" in subsequent NREM sleep (Peyrache et al. 2009). Similar results were reported in rats trained on a brain-machine interface. In this study, neuronal ensembles recruited in a learning task showed greater reactivation during NREM sleep after only a few learning trials (Gulati et al. 2014). One explanation for the difficulty in detecting novel experience during replay is that only a subset of neurons remodel during experience. For example, much of the activity of the sleeping hippocampus appears to be hardwired, but a subset of neurons are plastic. It is only the latter that change their activity during sleep in ways consistent with memory storage during replay (Grosmark and Buzsáki 2016).

Perhaps the largest caveat of the HND is that there has been little direct evidence that replay in sleep has any function. This situation is slowly changing. Two independent studies in rodents demonstrated that interrupting the hippocampal bursts that convey replay impairs maze-based learning (Ego-Stengel and Wilson 2010; Girardeau et al. 2009). The replay of the hippocampal neurons during sleep can also be triggered by reintroducing auditory tones present during experience, suggesting that replay represents a memory trace (Bendor and Wilson 2012). The imposition of waking patterns of activity (associated with a conditioned stimulus) in the olfactory bulb during sleep led to better performance in an aversive training task (Barnes and Wilson 2014). Interestingly, similar experiments in humans lead to greater performance on memory tasks (Schönauer et al. 2013), and spontaneous replay can predict future performance (Deuker et al. 2013). These results strongly suggest that replay induces adaptive, functional plastic changes in the brain, which is consistent with predictions of the HND.

5.3.2 The Synaptic Homeostasis Hypothesis (SHY)

The synaptic homeostasis hypothesis (SHY) proposes that sleep promotes global (or "net") synaptic weakening which offsets global synaptic strengthening that occurs

whenever an animal is awake (Tononi and Cirelli 2003, 2006, 2014). Although this formulation conflates a brain state (wakefulness) with processes that occur in brain states (plasticity), SHY does incorporate some interesting ideas. According to the SHY, synaptic weakening in sleep preserves the relative strength between synapses, allows for further synaptic changes, and prevents maladaptive metabolic costs associated with excessive synaptogenesis. The most recent description of SHY allows for subsets of synapses to be preserved against the downscaling process. This protection from down-selection still does not involve synaptogenesis or new synaptic strengthening during sleep. Therefore, all current iterations of the SHY predict that the *main* effect of sleep is a global reduction of synapse number or strength.

A number of findings are consistent with the SHY (but see Frank and Cantera 2014; Frank 2012). These include changes in proteins, synaptic efficacy, and synapse and dendrite morphology consistent with predictions of SHY (Vyazovskiy et al. 2008; Maret et al. 2011; Liu et al. 2010; de Vivo et al. 2017). In homogenized tissue, markers of synaptic potentiation (e.g., changes in AMPAR subunit number or phosphorylation) are higher in rats sacrificed at the end of the active phase (or after sleep deprivation), compared to animals sacrificed at the end of the rest phase (Vyazovskiy et al. 2008). Similar results are reported for measures of synaptic efficacy (EPSPs and mini EPSPs) and neuronal firing rates which are also elevated at the end of the active phase (or after sleep deprivation) relative to sleep (Frank and Cantera 2014; Vyazovskiy et al. 2008; Liu et al. 2010). Two imaging studies of cortical dendrite spine morphology showed that the ratio of spines eliminated vs. those formed was greater after sleep (Maret et al. 2011; Yang and Gan 2011). Interestingly, these results were restricted to stages of development when there is an overall pruning of synapses and were not detected in adult mice (Maret et al. 2011). It was also shown using electron microscopy in fixed mouse tissue (layer 2–3 of the cortex) that many synapses shrink in size when examined after a long period of sleep, relative to sleep deprivation or the wake phase (de Vivo et al. 2017). Similar morphological changes are reported in *Drosophila*. Synaptic proteins are elevated, and presynaptic structures, axonal arbors, and postsynaptic spines are more numerous after extended waking periods or sleep deprivation relative to sleep (Gilestro et al. 2009; Bushey et al. 2011; Donlea et al. 2011).

5.3.2.1 Reexamining the SHY

The SHY has emerged as one of the more popular theories of sleep function, yet there remain a number of important caveats. The first is that close inspection of all available evidence demonstrates that the effects of sleep on synaptic plasticity are far from uniform. They instead vary based on a number of factors, including the brain region under examination, the age of the animal, the types of waking experience that precede sleep, and the presence of strong circadian rhythmicity (Frank and Cantera 2014; Frank 2016; Areal et al. 2017). For example, the decrease in neuronal firing rates during sleep (that can be interpreted as support for SHY) does not occur in the visual cortex in juvenile and adult rodents (Aton et al. 2014; Hengen et al. 2016) or

developing cats (Aton et al. 2013). In the frontal cortex of rats, neuronal firing rates across bouts of sleep are inconsistent with only "selective down selection." Instead, sleep appears to promote firing rate adjustments consistent with preservation of the weaker synapses (Watson et al. 2016). Sleep has also been shown to increase *or* decrease cortical dendritic spines in adult mice, depending on the type of learning that precedes sleep and the cortical region under examination (Yang et al. 2014; Li et al. 2017). In the latter study increases in spine number are not accompanied by net reductions in other spines. In contrast to what is reported in the rodent cortex, extended wakefulness reduces morphological and biochemical markers of hippocampal synapses, events that are reversed during recovery sleep (Hagewoud et al. 2009; Havekes et al. 2007, 2016). This is also inconsistent with some synaptic strengthening against a background of net synaptic weakening.

The second caveat of the SHY is that virtually nothing is known concerning the sleep-dependent mechanisms that purportedly weaken synapses (Frank 2012, 2013). This stems in part from the fluid descriptions of what the SHY purportedly does to synapses, evident in the shifting name for the process involved. This has been variously described as "downscaling," "synaptic renormalization," and most recently "selective down selection" (Tononi and Cirelli 2003, 2006, 2014). Tononi and Cirelli have argued that the SHY involves mechanisms distinct from *synaptic scaling* as described by Turrigiano (Tononi and Cirelli 2012). These distinctions, however, are hard to detect in the original theoretical descriptions of the SHY. The weakening mechanism was specifically described as "synaptic downscaling" *as defined by* Turrigiano: "SWA, in turn, would promote synaptic downscaling (Turrigiano, 1999)" (Cirelli et al. 2005). Second, "synaptic renormalization" and "downscaling" have the same basic properties as synaptic scaling. Synaptic renormalization influences all or most synapses; it offsets LTP (or LTP-like plasticity). It involves a form of synaptic weakening that is proportional at each synapse (Tononi and Cirelli 2003, 2006). The consequences of unchecked synaptic potentiation in SHY are also similar to the network instability described in synaptic scaling: "Sleep, and the accompanying downscaling of synapses, would then be needed to interrupt the growth of synaptic strength associated with waking and prevent synaptic overload"(Tononi and Cirelli 2006). Most of these aspects of what one might call "canonical" synaptic scaling are retained in the most recent iteration of the SHY. The primary difference is the concept of "selective down selection," which differs from canonical scaling in that a proportional reduction at all synapses is no longer included. Instead, only "weak" synapses are downscaled during sleep (Tononi and Cirelli 2014).

No matter the name selected for the process in the SHY, it is useful to ask whether sleep is indeed conducive for canonical synaptic scaling. As first pointed out by Tononi and Cirelli, neural changes that occur across the sleep-wake cycle appear inconsistent with synaptic downscaling during sleep (Tononi and Cirelli 2001). This has turned out to be a prescient, if abandoned, insight. For example, Tononi and Cirelli propose that overall cortical activity decreases during NREM sleep, which downscale synapses. However, according to canonical synaptic scaling, global suppression in neuronal activity *upscales* synapses, while overall enhancement in neuronal activity downscales synapses. Therefore, overall neuronal suppression

during NREM sleep should upscale synapses. Similarly, the neural expression of scaling factors (BDNF, Arc, and tumor necrosis factor [TNFα]) across the sleep-wake cycle is inconsistent with downscaling during sleep (Frank 2012; Tononi and Cirelli 2001). While it has been recently reported that Homer 1a mediates synaptic downscaling during sleep, this study did not examine sleep per se. It instead measured changes in synapses at two vastly different times of day in a strongly circadian species (mice) in the absence of quantitative measures of sleep or wakefulness or controls for circadian influences (Diering et al. 2017). Therefore the results may be equally due to sleep or circadian rhythms.

Surprisingly, the one true test of canonical synaptic scaling in sleep found that sleep inhibited this form of plasticity (Hengen et al. 2016). In this study, single-unit activity was chronically recorded from monocular visual cortex in developing rats during the critical period for visual development. During the critical period, MD initially reduces spontaneous unit firing rates, but over the next 2 days, firing rates recovered to baseline values. This process is consistent with synaptic upscaling. Intriguingly, upscaling only occurred when the rats were awake and active. No upscaling could be detected in REM or NREM sleep. This was true whether analyzed in the light or dark phase, indicating that this process was not driven by endogenous rhythms. Thus, at least one form of canonical synaptic scaling in vivo does not occur during sleep.

These findings collectively suggest that canonical synaptic scaling does not operate during sleep in a manner consistent with the SHY. What other mechanisms might be important? NREM SWA has been proposed to directly weaken synapses (Tononi and Cirelli 2003, 2006). This role has become opaque over the years, as SWA is also considered sometimes an "index" (Tononi 2009) or "sensor" of synaptic potentiation (Tononi and Cirelli 2012). It is not clear in the SHY when SWA should be treated as a "sensor," "index," or active mechanism for synaptic weakening. More importantly, there is no direct evidence that cortical SWA can weaken synapses (Frank 2012; Steriade and Timofeev 2003), while several studies indicate that SWA might strengthen synapses. Visual cortical EPSPs do not decline across sleep, and peaks in NREM SWA precede increases in EPSPs. These results have been interpreted as a form of synaptic potentiation (Tsanov and Manahan-Vaughan 2007). Consistent with these observations, cortical postsynaptic potentials in vivo are potentiated after a period of NREM SWA, but not wakefulness. In addition, experiments in vitro which simulated SWA specifically led to synaptic potentiation, while simulations of waking activity did not. Watson et al. (2016) also find that NREM SWA is not accompanied by a selective down selection of synapses (at least, as inferred by changes in firing rates) (Watson et al. 2016).

To summarize, it is not yet clear if the synaptic changes reported after sleep in support of the SHY reflect an active sleep-dependent mechanism. They could instead be caused by other factors, including independent circadian rhythms in hormone release or brain temperature (for review, see Frank and Cantera 2014; Frank 2016). As one example, circadian changes in brain temperature alone may explain the morphological changes in synapses reported after sleep in rodents. This is because such changes fall on a continuum that occurs in brain states associated with changes in

brain temperature (Heller and Glotzbach 1977). The most extreme drops in brain temperature (e.g., in hibernation) result in dramatic shrinkage of synaptic structures in hibernating rodents which grow back during euthermia (von der Ohe et al. 2007; Popov and Bocharova 1992). This is strikingly similar, but of *larger* scale, to what has been reported in layer 2/3 neurons in nonhibernating rodents presumably during sleep (de Vivo et al. 2017). Nonhibernating rodents also normally experience a significant, but *smaller* scale, drop in brain temperature during sleep, a process driven by biological clocks (Frank 2016).

The final caveat to the SHY is that there is no convincing direct evidence that the synaptic weakening cited in support of this idea has any function (Tononi and Cirelli 2014). This is in contrast to the HND, where, as discussed above, an increasing number of studies are beginning to show that replay, or the brain waves that carry replay, is functional. The evidence that neural changes ascribed to the SHY have any function is based almost entirely on computational models (Hill et al. 2008; Olcese et al. 2010; Nere et al. 2013), not real biological findings. Computational models can inform neurobiology but are not substitutes for neurobiology. They depend critically on what variables are included in the model and the assumptions one makes about how actual neurons operate in vivo. There are other computational models of memory consolidation which also posit a role for sleep that does not employ "selective down selection" or "renormalization" as described in SHY (O'Donnell and Sejnowski 2014; Blanco et al. 2015). Therefore, *direct* tests of how downscaled synapses lead to adaptive changes (behaviorally or otherwise) are still absent.

5.4 Concluding Remarks

Converging lines of evidence support the idea that sleep influences brain plasticity. There remain, however, a number of unresolved issues. The underlying mechanisms are still undefined, and the results of "bottom-up" approaches have not been fully integrated into current theories of sleep function. Having said that, the HND is consistent with our current understanding of synaptic plasticity and can account for many basic findings. The HND was originally conceptualized in terms of Hebbian LTP and LTD, in that the bursts of activity originating from the hippocampus if properly timed with postsynaptic targets would lead to synaptic potentiation according to Hebbian rules and cellular mechanisms of LTP. The more recent formulations of the HND include a two-way flow of information in the hippocampus, with cortical inputs driving or influencing replay and sharp-wave events. This, in turn, may require additional plastic changes within the hippocampus itself, which can explain why hippocampal LTP may be promoted during sleep. It also appears that a basic component of the HND ("replay" or "reactivation") is not restricted to the hippocampus, but can occur in many brain areas during sleep (Frank 2007), including the visual cortex (Dumoulin Bridi et al. 2015; Ji and Wilson 2007). There is nothing in the HND that precludes many findings derived from bottom-up approaches. The HND or its variants are also consistent with findings using classic models of memory or plasticity in the hippocampus and visual cortex.

In contrast, the SHY has yet to present a clear mechanism or set of mechanisms available for investigation that similarly incorporate disparate findings in the field. An inclusive review of the available literature does not always find a net effect of sleep on synaptic number or strength (Frank and Cantera 2014). Nor are there any compelling *biological* findings demonstrating that "renormalization" or "selective down selection" can account for the increasingly clear evidence that synapses can strengthen or form during sleep without net weakening. It may be tempting (and perhaps convenient) to dismiss these troublesome data in various ways (Cirelli and Tononi 2015; Tononi and Cirelli 2014), but this will not provide any deep insights into sleep function. Instead, provided that the basic principles of the SHY are true, the more fruitful strategy will be to find ways to reconcile the SHY with the basic concepts of the HND.

The second challenge is to resolve the debate over what constitutes the best approach to solving this problem. Few experimental paradigms perfectly capture what happens in the intact animal (Holscher 1999; Albensi et al. 2007). For example, LTP in vitro often involves types of stimuli not normally encountered by animals (e.g., electrical tetany via an imbedded electrode) and preparations that lack many features of the whole brain (e.g., an absence of neuromodulators, intact circuitry, blockade of inhibition) (Holscher 1999; Albensi et al. 2007). Accordingly, plasticity is considered "nonphysiological" when it involves forms of stimulation not naturally experienced by the intact brain or measurement conditions that do not reproduce the conditions of the intact brain (Holscher 1999; Albensi et al. 2007). To illustrate this point, some studies cited as evidence for the SHY employ nonphysiological approaches, including exogenous, transcallosal electrical stimulation (Vyazovskiy et al. 2008), intracranial infusions of chemicals that cause cortical spreading depression (Faraguna et al. 2010), intracortical infusions of neurotrophins and antibodies (Faraguna et al. 2008), transcranial electromagnetic fields (Huber 2007), and measurements in vitro that require the use of tetrodotoxin and picrotoxin (Liu et al. 2010). None of these conditions occur naturally. More physiological approaches used to test predictions of the SHY include experimental manipulations of sensory experience that are similar in principle as used to induce ODP. These include arm immobilization (Huber 2006) and training rodents to reach with one limb (Hanlon et al. 2009), procedures which either reduce sensory input in one pathway or increase it in another. Similarly, ODP is considered physiological because it occurs naturally in the intact brain in response to changes in sensory input in one pathway vs. another. It would seem, therefore, that the productive strategy is to recognize that all experimental approaches to understanding brain plasticity are limited and provide, at best, an approximation of what actually occurs in the intact brain.

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Chapter 6
The Role of Sleep in Emotional Processing

Daniela Tempesta, Valentina Socci, Luigi De Gennaro, and Michele Ferrara

Abstract In this chapter, we have reviewed an extensive literature supporting the critical role of sleep for several aspects of emotional processing and regulation.

In the first part, we discussed the main behavioral and psychophysiological studies that examined how sleep influences the processes of encoding and consolidation of emotional memory. In addition, we examined how sleep modulates emotion regulation, emotional reactivity, and empathy. Further, we discussed the implication of sleep in fear conditioning memory, threat generalization, and extinction memory. In the second part, we discussed evidence specifically suggesting the implication of REM sleep in the consolidation of emotional memory and in the modulation of emotional reactivity. In particular, we will focus on the specific physiological REM features that contributed to suggest its critical involvement in emotional processing. In the third part, we overviewed the functional neuroimaging studies on the brain mechanisms that underlie the relations between sleep and emotions. Finally, we focused on the most important psychiatric disorders that express abnormalities of sleep and emotional alterations, briefly reviewing our knowledge about the relationships between sleep disturbances and mood in major depression, anxiety disorders, and post-traumatic stress disorder.

We showed that sleep helps in the formation of emotional memories at every stage of this process. On the contrary, sleep loss induces deficit in encoding of emotional information, leading to a disruptive interference with emotional memory consolidation. The reviewed literatures clearly suggest that sleep loss significantly influences emotional reactivity. Whether sleep acts to protect, potentiate, or de-potentiate emotional reactivity is, however, still debatable. Future studies will have to elucidate, at the behavioral level, the specific direction of the sleep-dependent emotional modulation. Sleep seems to be crucial also for our ability to correctly process emotional information that allows us to understand the others'

D. Tempesta · V. Socci · M. Ferrara (✉)
Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy
e-mail: michele.ferrara@univaq.it

L. De Gennaro
Department of Psychology, Sapienza University of Rome, Rome, Italy

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feelings and to be empathic with them, as well as for our ability to encode and consolidate fear conditioning and extinction learning. As far as the role of REM sleep is concerned, it seems to be crucial for the consolidation of emotional memory, while its specific contribution on next-day emotional reactivity is less clear. In fact, REM sleep could act to potentiate or, conversely, de-potentiate the emotional charge associated to a memory along with its consolidation. This topic could be also relevant for its implications in clinical settings. Indeed, further explaining how sleep influences the next-day emotional brain functioning will be crucial to open a new perspective for the understanding and treatment of affective or anxiety disturbances in patients with disturbed sleep.

Keywords Emotional memory · Emotional reactivity · Empathy · Fear conditioning · REM sleep · Sleep deprivation

6.1 Introduction

In the modern Western societies, sleep is often considered a period of wasted time that might be better devoted to more productive activities. However, we spend on average about one-third of our lives asleep. Sleep is a universal need of all higher life forms including humans, the absence of which has serious cognitive and physiological consequences.

Research over the past years has shown the key function of sleep in several human abilities that mainly involve the frontal cortex, such as executive functions and working memory (Jones and Harrison 2001; Durmer and Dinges 2005), and the limbic areas, such as emotional processing (Payne and Kensinger 2011). However, even though the crucial role of sleep in the consolidation and integration memory processes is nowadays largely acknowledged, an unequivocal hypothesis about the specific role of sleep in affective and emotional processing is still lacking. Nevertheless, a number of recent evidence evaluating the effects of sleep loss on emotional reactivity (e.g., Zohar et al. 2005; Yoo et al. 2007; Tempesta et al. 2010) and emotional memory (e.g., Sterpenich et al. 2007, 2009; Tempesta et al. 2014, 2015, 2016) showed behavioral and functional alterations imposed by sleep loss.

The goal of this chapter is to provide a synthesis of these recent findings in humans, analyzing in detail the role of sleep in the different components of emotional processing. In the first section, the relations between sleep and emotions will be discussed. Particularly, we describe the main behavioral and psychophysiological studies that investigated the influence of sleep in the emotional memory encoding and consolidation processes. Thereafter, we have discussed how sleep modulates emotions. We have particularly reviewed relevant evidence regarding the role of sleep in emotional reactivity and in more complex emotional processes, such as those involved in empathy. Furthermore, we have specifically discussed the role of REM sleep in emotional memory consolidation and emotional reactivity, analyzing

the specific physiological features of REM that contributed to suggest its critical implication in emotional processing. In the third section, we have further discussed the relations between sleep and emotions by overviewing the functional neuroimaging studies on the brain mechanisms that underlie these processes. It can be observed, particularly during REM sleep, the activation of brain areas specifically involved in human emotional processing. It provides new insights into the protective role of sleep in human emotional homeostasis and emotional regulation. Finally, we turn our attention to the most important psychiatric disorders that express co-occurring sleep disorders and emotional alteration, briefly reviewing our knowledge about the relationships between sleep disturbances and mood in major depression, anxiety disorders, and post-traumatic stress disorder.

6.2 The Relations Between Sleep and Emotions: Behavioral and Psychophysiological Studies

Sleep is traditionally defined as a reversible behavioral state of perceptual disengagement from and unresponsiveness to the environment. Sleep comprises two separate states which largely differ on the basis of a constellation of physiologic parameters. These two states, rapid eye movement (REM) and non-rapid eye movement (NREM), exist in virtually all mammals, and they are as distinct from one another, as well as each one is from wakefulness.

The normal human adult enters sleep through NREM sleep. REM sleep does not usually occur until subject experience on an average 80 min or longer episodes of NREM sleep. Thereafter, NREM and REM sleep alternate through the night, with about a 90-min cycle. Both sufficient sleep continuity and sleep duration are prerequisites for recuperation and may be considered as a "restart" at many neurophysiological levels (Kahn et al. 2013).

It has been claimed that the ideal amount of sleep in healthy young adults is around 8 h per night (Ferrara and De Gennaro 2001). Deficits in daytime performance due to sleep loss are experienced universally. The first published experimental study about the effect of total sleep deprivation on cognition in humans dates back to 1896 and found that memory was significantly deteriorated after 90 h of continuous wakefulness (Patrick and Gilbert 1896). Since that time, hundreds of more detailed and systematic studies have been conducted. Most of this work has been conducted on normal, healthy individuals in the context of total sleep deprivation paradigms.

To date, it has been demonstrated that sleep deprivation significantly affects human functioning (Pilcher and Huffcutt 1996; Boonstra et al. 2007), negatively influencing levels of alertness and cognitive performance (Harrison and Horne 2000; Thomas et al. 2000; Wesensten 2006; Couyoumdjian et al. 2010; Killgore 2010).

In the last two decades sleep deprivation method has widely been used to investigate the relationship between sleep and learning/memory consolidation (see

Gais and Born 2004; Walker 2008). In such studies, participants typically learn a task prior to a good night sleep or a night of sleep deprivation. All participants are tested following one or two nights of recovery sleep to minimize any residual effects of acute sleep loss. Research in this area has been extremely fecund and has improved our understanding of how sleep loss can affect memory consolidation processes (Drummond et al. 2006; Sterpenich et al. 2009; Goulart et al. 2014). Within this framework, how sleep is beneficial for the consolidation of declarative and procedural memories has been demonstrated convincingly (Smith 2001; Walker and Stickgold 2004; Backhaus and Junghanns 2006; Marshall and Born 2007; Tucker and Fishbein 2009).

An extensive literature in the last years has provided evidence that sleep likewise supports emotional memory consolidation (Wagner et al. 2006; Hu et al. 2006; Cairney et al. 2015; Tempesta et al. 2015; Genzel et al. 2015), while sleep deprivation negatively affects it (Atienza and Cantero 2008; van der Helm et al. 2011; Morgenthaler et al. 2014; Tempesta et al. 2014, 2016). Empirical evidence suggests that the emotional strength of the material learned can modulate memory processing. In fact, emotional information is often remembered more accurately and persistently than nonemotional information (Kensinger 2004). Therefore, emotional load intensifies the subjective sense of remembering, enhancing our memory.

Here we will show that sleep supports the consolidation also of this particular type of memory. In particular, the following paragraphs propose a review of the body of research on the impact of sleep and sleep loss on emotional memory processing, emotional reactivity (e.g., Zohar et al. 2005; Tempesta et al. 2010), empathy (e.g., Guadagni et al. 2014, 2016), and fear conditioning (e.g., Milad and Quirk 2012).

6.2.1 Sleep and Emotional Memory Processing

Memory appears to develop over time into three distinct processes: memory encoding, memory consolidation, and finally memory retrieval. The "encoding" process refers to the uptake of information to be stored into a representation. The "consolidation" process refers to a post-encoding process in which the newly encoded representation, which is initially fragile and prone to decay, is transformed into a more stable and longer-lasting representation. Finally, the "recall" refers to the reactivation of the stored memory to enable the execution of an adaptive response in appropriate environmental contexts (Westermann et al. 2015).

Over the past decade, substantial evidence has been provided supporting the role of sleep in memory processing. This process is now referred to as "sleep-dependent memory processing." In the following sections, we describe how sleep is specifically implicated in all stages of the processing of emotional traces.

6.2.1.1 Emotional Memory Encoding

Most of the studies that investigated the relationship between sleep and human memory examined the influence of sleep on post-training consolidation, more than on the initial encoding stage. However, it has been likewise demonstrated that sleep deprivation negatively affects the ability to encode episodic information (Drummond et al. 2000; Walker and van der Helm 2009; Kaida et al. 2015).

As far as emotional memory is specifically concerned, the role of sleep on encoding of emotional information has only recently received attention. Only two studies till date (Kaida et al. 2015; Tempesta et al. 2016) have examined the impact of pre-training sleep or sleep loss on emotional memory formation.

Kaida and coworkers (2015) compared the effects of total sleep deprivation and of selective REM sleep deprivation on the subsequent encoding of neutral and emotional pictures. Encoding capabilities were examined, after each experimental night, by administering a picture recognition test right after encoding. A total sleep deprivation alters the ability to encode emotional pictures, but not the selective REM sleep deprivation, suggesting an essential role of NREM rather than REM sleep in encoding the emotional memory processes (see Sect. 6.3 below for a detailed evaluation of the relations between REM sleep and emotional memory). These results also suggest a proactive role of sleep deprivation in affecting emotional memory encoding.

In a recent study, we investigated the impact of sleep deprivation on emotional memory encoding of both contextual and non-contextual material (Tempesta et al. 2016). Contextual memory involves the retrieval of precise details associated with a test item, whereas non-contextual memory involves retrieval of a simple fact that an item has been encountered previously and nothing much can be recalled about its prior occurrence (Wixted et al. 2010). Subjects were sleep deprived for one night or allowed to sleep normally prior to an emotional memory encoding session in which six clips of films of emotionally negative, positive, and neutral valence were presented. In addition, after two nights of recovery sleep, all subjects performed a recall session, in which the non-contextual emotional memory was assessed by a recognition task, while the contextual emotional memory was evaluated by a temporal order task. The results suggest that sleep deprivation significantly impairs the encoding of both contextual and non-contextual aspects of memory, and it caused a significantly weak retention 2 days later. Interestingly, the sleep-deprived subjects were able to recognize the negative non-contextual events, suggesting that the encoding of negative stimuli is more "resistant" to the disruptive effects of sleep deprivation (Tempesta et al. 2016). The latter finding is in line with an established literature that demonstrates that memory processing can be modulated by the emotional strength of the material learned (see McGaugh 2004; Phelps 2004). In fact, memories with negative emotion are encoded strongly and persist longer than neutral memories.

In summary, the above reviewed studies indicate that sleep plays an essential role for the emotional memory encoding; on the other hand, lack of sleep leads to a disruptive interference with emotional memory consolidation and to the ensuing decay of instable memory traces.

6.2.1.2 Emotional Memory Consolidation

A growing body of research supports the role of sleep in memory consolidation (for a review, Born and Wilhelm 2012). An equally high number of studies suggest that sleep plays a selective and crucial role also in the consolidation of emotional memories (e.g., Holland and Lewis 2007).

The emotion may strongly modulate consolidation. The neutral memories are gradually lost over time (McGaugh 2000; Frankland and Bontempi 2005), but emotional memories are subjected to such loss to a lesser extent (LaBar and Cabeza 2006). Converging evidence indicates that sleep-based consolidation processes are crucial for the long-term maintenance of emotional information (Diekelmann et al. 2009).

In a series of behavioral studies, Wagner and colleagues have reported that the post-learning sleep has a positive influence on the retention of emotional memory contents (Wagner et al. 2001, 2006). In the first study, subjects learned neutral or emotional texts immediately before a 3-h period of wakefulness or sleep, allowed during the first or the second half of the night (Wagner et al. 2001). It was found that sleep selectively favors the retention of previously learned emotional texts relative to neutral texts. In the following study, it was demonstrated that this emotional memory enhancement persists for several years (Wagner et al. 2006). The participants were the same of the previous study (Wagner et al. 2001), recontacted after 4 years for a long-term memory assessment by means of a forced-choice recognition test. Results demonstrated that brief periods of sleep immediately following learning had led to the preservation of emotional memories over several years. However, similar memory enhancement for neutral texts was not observed. This indicates that emotional memory formation, relative to the neutral one, benefits more from the long-lasting effect of sleep after learning.

Hu and colleagues (2006) examined the impact of 12 h of sleep or wakefulness on memory for negative arousing and neutral pictures, using a recognition memory task that requires to discriminate between the original pictures and novel pictures by responding "remember," "know," or "new." In this paradigm, a list of pictures was shown to the subjects initially, and subsequently they were asked to judge test stimuli as the original or novel pictures by using the three abovementioned responses. The response "remember" indicated that the recognition of the picture was associated with retrieval of specific contextual details during encoding. The response "know" was associated with the feeling of familiarity or the definite feeling of having encoded the item, but without being able to retrieve any further specific details. The response "new" was given when the participant thought that the item had not been presented during encoding. It was observed that one night of sleep selectively improved memory accuracy for negative arousing pictures compared to

an equivalent period of daytime wakefulness, but only for "know" judgments (Hu et al. 2006). Moreover, the participants became more conservative when making "remember" judgments, especially for emotionally arousing pictures, across a night of sleep compared to a period of wakefulness. These findings suggest that the sleep selectively facilitates the consolidation of emotional memory, as indicated by the preferential overnight enhancement of both recognition accuracy and emotional bias (Hu et al. 2006).

In agreement with these results, Baran et al. (2012) performed a recognition memory task during two sessions separated either by 12 h of daytime wake or 12 h including overnight sleep and confirmed that recognition memory was better following sleep compared with a wake period of the same length. Moreover, the accuracy was higher following sleep relative to wake for both negative and neutral pictures (Baran et al. 2012).

Interestingly, Payne and colleagues observed that even a short nap in the afternoon sufficiently triggers preferential memory consolidation for emotional information associated with complex scenes (Payne et al. 2015). Along the same vein, the recent work of Cellini and colleagues indicated that a daytime nap facilitates both the consolidation and the post-sleep encoding of declarative memories, but regardless of their valence (Cellini et al. 2016).

In the last few years, some studies using the sleep deprivation paradigm have provided further evidence in support of the sleep-dependent emotional memory consolidation (Atienza and Cantero 2008; Tempesta et al. 2015). In the first of these studies, the participants were sleep deprived the night immediately following the exposure to emotional and nonemotional images, whereas the control group slept at home (Atienza and Cantero 2008). Memory was tested 1 week later with a recognition task. Sleep deprivation resulted in behavioral impairment at retrieval of both emotional and neutral images. Moreover, the subjective experience of remembering the specific details associated with test images was selectively impaired by the loss of sleep, whereas the subjective experience of just knowing that an item was previously encountered, even though nothing specific about its prior occurrence can be recalled, remained unaffected. These findings can be interpreted as a demonstration that sleep deprivation interferes with conscious contextual retrieving of old events in general, but not with non-contextual retrieving of stored information.

In a recent study from our group, sleep-deprived subjects were compared to subjects with poor sleep quality and with a normally sleeping control group, to test the hypothesis that sleep loss is associated with a lower recall of emotional stimuli (Tempesta et al. 2015). Twenty-four hours after the encoding session, all subjects were requested a yes/no memory judgment of the target pictures previously encoded ("old pictures"), intermingled with nontarget pictures ("new pictures"). We showed that individuals having poor sleep can preserve sleep-dependent consolidation of emotional information and demonstrate the same post-sleep performance accuracy as good sleepers. On the other hand, one night of sleep deprivation results in a reduced ability to recall emotional information successfully. These findings are

consistent with previous research revealing the positive effects of sleep on emotional memory consolidation (Wagner et al. 2001, 2006; Hu et al. 2006; Baran et al. 2012).

Altogether, these studies indicate that a period of (even brief) sleep is needed for the consolidation of emotional memory and that sleep quality does not significantly influence this relation. Thus, the sleeping brain seems to provide ideal conditions for emotional memory consolidation.

6.2.2 Sleep and Emotional Reactivity

Individuals differ remarkably in their emotional reactivity, that is, the quality and intensity of response to affectively evocative stimuli (Wheeler et al. 1993). Emotional reactivity can be measured along two dimensions: arousal (ranging from calm to excitement) and valence (ranging from positive to negative, with neutral often considered an intermediate value) (Lang et al. 1993; Labar and Cabeza 2006).

The International Affective Picture System (IAPS) is a validated set of visual stimuli widely used in experimental studies for evaluating emotional reactivity (Lang et al. 1998). In these studies, the subjects are typically asked to subjectively report the valence and arousal of their emotional reactions to affective pictures. These two dimensions in emotional perception have been found to correlate with facial muscle activity, skin conductance, heart rate, and startle response (Lang et al. 1998), suggesting a consistent pattern in adults' verbal, behavioral, and physiological responses to the affective pictures contained in the IAPS (Bradley et al. 1990, 2001; Lang et al. 1993, 1998).

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It is widely known that sleep modulates emotion regulation. In this respect, sleep loss causes mood changes and increases subjective irritability and affective volatility (Horne 1985; Rosen et al. 2006). For example, Dinges and colleagues (1997) have reported that with 5 h of sleep depriving per night, individuals develop a progressive increase in emotional disturbance across a 1-week period on the basis of subjective mood scales (Dinges et al. 1997). Accordingly, a meta-analysis of the effects of sleep deprivation has demonstrated that mood is more affected than cognitive or motor performance with sleep loss (Pilcher and Huffcutt 1996).

While the effects of sleep loss on mood are largely documented, the explicit impact of sleep deprivation on subjective reactivity to emotional stimuli has been less taken into account (Wagner et al. 2002; Zohar et al. 2005; Franzen et al. 2009; Lara-Carrasco et al. 2009; Tempesta et al. 2010; Baran et al. 2012; Groch et al. 2013; Cunningham et al. 2014). Moreover, these studies reported discordant results.

Baran et al. (2012) investigated how nocturnal sleep, compared to a period of daytime wakefulness, modulates subjective ratings of valence and arousal to negative pictures. They demonstrated an attenuation of negative ratings after 12 h of

daytime wakefulness, whereas a relative maintenance of the initial negative ratings was associated with a period of 12 h including sleep. That is, a picture that was initially deemed highly negative was rated as substantially less negative following 12 h awake, but only mildly less negative following sleep. These differential changes of emotional reactivity across periods of waking vs. sleep were interpreted as related to a habituation effect, therefore suggesting that sleep would facilitate habituation (Baran et al. 2012). Likewise, Groch et al. (2013) suggested that sleep does not modify the emotional reactivity associated with emotional stimuli. Indeed, they observed that valence and arousal ratings of emotional pictures were not affected by REM-rich or SWS-rich sleep.

Interestingly, in this study the analyses of ERPs revealed increased positivity in response to negative pictures in the frontal late positive potential (300–500 ms poststimulus onset), confirming the notion that subjective and objective parameters may not converge in experimental paradigms dealing with emotional responses (Groch et al. 2013).

At variance with the previous studies, reporting minor or no changes in emotional reactivity after a night of sleep, Wagner et al. (2002) suggested that sleep increases this reactivity. They assessed the emotional reactions by a nonverbal rating procedure along the two emotional dimensions of valence (positive vs. negative) and arousal (low vs. high). Two groups of healthy men were tested across 3-h periods of early and late nocturnal sleep or corresponding intervals filled with wakefulness. After the 3-h intervals, subjects rated new pictures mixed together with pictures already presented before. Subjective ratings of the negative valence following sleep resulted more negative for pictures viewed before sleep compared to new, unfamiliar pictures. This study, hence, demonstrates that sleep can mediate emotional reactivity and also highlights that this reactivity to an aversive event is differentially affected, depending on whether it is novel or familiar (Wagner et al. 2002). Similarly, Lara-Carrasco et al. (2009) showed that REM sleep deprivation alters emotional evaluation, in particular reducing reactivity to the negative valence of stimuli. From this, the authors argue that REM sleep enhances aversive reactivity to negative pictures. Altogether, the last two studies suggest that sleep may protect or even potentiate emotional reactivity.

In disagreement, Cunningham and colleagues (2014) have observed a general de-potentiating effect of sleep. They have shown a decrease of visceral reactivity to both negative and neutral objects following sleep. Interestingly, it has been observed that the arousal responses to negative scenes at encoding increased significantly (as measured by heart rate deceleration and skin conductance responses), which positively correlated with subsequent memory for the negative objects of scenes, but only for the subjects that had slept. This indicates that larger psychophysiological reactions to negative pictures at the time of encoding may "tag" the preferential consolidation of these images during subsequent sleep.

Other studies turned their attention to the effects of sleep loss on our responses to emotional stimuli. We all know that inadequate sleep potentiates the negative reactions to adverse experiences; at the same time it reduces the positive reactions to pleasant events. In this respect, Zohar et al. (2005) suggested that these effects on

emotional reactivity can have implication for real-word settings. In their study, they investigated the effects of sleep disruption on emotional reactivity to daytime work events in medical residents. Emotional reactivity was measured using the experience-sampling methodology. For 3 consecutive days, residents received three phone calls at random times during their working day. The residents were reminded through these calls to fill out brief questionnaires concerning change of circumstances over the previous 15 min and to rate their emotional response to these circumstances, as well as fatigue. It was found that sleep loss augmented negative emotional consequences in response to disruptive daytime events and has blunted the positive benefit underlying rewarding or goal-enhancing activities (Zohar et al. 2005).

We have also found a similar role of sleep debt as a potentiating factor of emotional reactivity (Tempesta et al. 2010). We investigated in healthy subjects the effects of one night of sleep deprivation, compared to those of one night of undisturbed sleep at home, on subjective ratings of the emotional valence and arousal of pleasant, neutral, and unpleasant pictures. Results showed that sleep-deprived subjects evaluate the neutral pictures in a more negative way compared to the subjects that slept at home. At the same time, both groups evaluate similarly the negative pictures, suggesting that sleep loss does not alter the assessment of negative stimuli. Similarly, there were no significant differences between groups in the valence ratings for pleasant pictures. Such a more negative valence rating of neutral pictures after sleep deprivation indicates that sleep subtly affects emotional evaluations. Indeed, sleep-deprived subjects did not change their judgment of explicitly positive and negative stimuli. Moreover, we found that the emotional labeling of neutral stimuli biased toward negative responses was not mediated by the increase of negative mood that typically accompanies sleep loss, indicating that sleep per se is involved in regulating emotional evaluations (Tempesta et al. 2010).

Emotional reactivity under the condition of sleep deprivation has been also measured by pupillography (Franzen et al. 2009). Although sleep deprivation did not significantly impact on subjective ratings, sleep-deprived subjects showed larger pupillary responses during the interstimulus interval following neutral trials compared to non-sleep-deprived subjects. This finding further suggests that sleep loss increases reactivity to the emotionally unloaded stimuli, in line with the results by Tempesta and coworkers (2010).

Therefore, the influence of sleep (and of its specific stages) on emotional reactivity remains not yet fully established (see below Sect. 6.3 for a detailed analysis of the studies on REM sleep), given the contradictory results of the few available studies reviewed in this section (Wagner et al. 2002; Lara-Carrasco et al. 2009; Baran et al. 2012; Groch et al. 2013; Cunningham et al. 2014). The discrepancies can be attributed to several methodological factors, including different sleep protocols. In this respect, some studies have shortened total sleep time (Wagner et al. 2002; Lara-Carrasco et al. 2009; Groch et al. 2013), while others allowed a whole night of undisturbed sleep (Baran et al. 2012; Cunningham et al. 2014). Moreover, it should be noted that the paradigm of Wagner et al. (2002) and Groch et al. (2013) relies on the differential distribution of the critical sleep stages, SWS and REM sleep, across

the early and late halves of the night. The elicitation of different emotional responses could also be because of differences in the tasks. In fact, Cunningham et al. (2014) have created different scenes containing emotional or neutral objects, whereas in all the other studies, the pictures have been taken from the International Affective Picture System. Thus, the different stimuli that can differently impact emotional reactivity, resulting in a confounding factor, cannot be ruled out. It should also be noted that many of the above results are based on subjective ratings that may be biased toward what participants think they should be feeling, more than what they actually experience (Cunningham et al. 2014). A coherence of subjective ratings and objective measures (behavioral or psychophysiological) is not guaranteed when emotional responses are taken into account (e.g., Franzen et al. 2009; Baran et al. 2012; Groch et al. 2013).

On the other hand, literature on the total sleep deprivation converges in support of the hypothesis that sleep loss significantly influences affective appraisal (Zohar et al. 2005; Franzen et al. 2009; Tempesta et al. 2010). Sleep loss indeed seems to cause a negative bias in the categorization of emotionally unloaded stimuli (i.e., neutral pictures) or in an increased emotional (subjective and autonomic) reaction to these stimuli.

Two different hypotheses have been proposed to explain the specific functions of sleep in the modulation of emotional processing. The hypothesis put forward by Walker (2009) and Walker and van der Helm (2009), currently dominating the field, suggests that when emotional memories are consolidated over sleep, the negative emotional tone is simultaneously attenuated. On the other hand, Wagner speculates that, as sleep enhances consolidation of the emotional memory, its emotional valence will also be maintained (Wagner et al. 2006). Both hypotheses will be examined in more detail in Sect. 6.3.

6.2.3 Sleep and Empathy

One of the major functions of our brain is to enable us to interact successfully in social groups. The ability to understand and share another person's mental state in terms of emotions, feelings, and thoughts has a key role for successful interactions (Shamay-Tsoory 2011). This capacity is referred to as "empathy." For example, if a person views a sad person and consequently feels sad, that subject is experiencing empathy.

It has been suggested that empathy includes two dimensions (Decety and Meyer 2008; Singer 2006): the cognitive component, also known as "theory of mind," consisting of the ability to understand and explain the mental states of others (Gallese 2007; Shamay-Tsoory 2011), and the emotional component, referring to the individuals' own experience of the others' actual or inferred emotional state (Davis et al. 1994; Dziobek et al. 2011). In addition to this bidimensional categorization of empathy, Dziobek and collaborators (2008) proposed a double dissociation

within the emotional empathy dimension: the explicit emotional empathy (rating of empathic concern) and the implicit emotional empathy (arousal ratings as a proxy for empathic concern).

Several previously revised studies provide clear evidence that sleep deprivation is detrimental to mood (Dinges et al. 1997) and emotional processing (Zohar et al. 2005; Tempesta et al. 2010; Baran et al. 2012), leading to an increase of the propensity of the individuals to assess the emotions more negatively (Tempesta et al. 2010) and to an amplification of the sympathetic responses (e.g., pupillary dilation) triggered by negative stimuli (Franzen et al. 2009). In addition, by measuring in healthy adults the intensity of facial expressiveness after one night of total sleep deprivation, Minkel et al. (2011) showed that sleep-deprived subjects resulted less emotionally expressive in response to both positive and negative emotional video clips (Minkel et al. 2012). Another study investigating the impact of sleep deprivation on the ability to recognize the intensity of human facial emotions observed that sleep deprivation selectively impairs the accurate judgment of angry and happy human facial emotions (van der Helm et al. 2010). These results are important because the recognition of facial expressions serves as an objective indicator of emotional functioning, also playing a critical role in communicating private emotional states, regulating social interactions, and even influencing subjective and physiological components of emotion (Levenson et al. 1990). Interestingly, sleep-deprived people are rated as less healthy and less attractive compared with when they are well rested, suggesting that humans are sensitive to sleep-related facial cues (Axelsson et al. 2010).

Therefore, sleep loss may have significant negative effects also on more complex emotional processes, such as those involved in empathy. To date, very few studies have investigated the relationship between sleep and empathy. Killgore and coworkers were the first to assess the effects of 55 h of sleep deprivation on perceived emotional intelligence of normal volunteers using the Emotional Quotient (EQ) inventory (Killgore et al. 2008). This self-report inventory measures self-perceived emotional intelligence and the underlying factors that contribute to emotionally intelligent behavior, which are at the basis of empathy. Relative to baseline, sleep deprivation was associated with lower total EQ scores, indicating a decreased global emotional intelligence. Analysis of the subscale scores showed that this decline in perceived emotional intelligence involved significant decreases on intrapersonal functioning (reduced self-regard, assertiveness, sense of independence, and self-actualization), interpersonal functioning (reduced empathy toward others and quality of interpersonal relationships), and stress management skills (reduced impulse control and difficulty with delay of gratification).

More recently, Guadagni and colleagues specifically evaluated the effects of sleep deprivation (Guadagni et al. 2014) and sleep quality (Guadagni et al. 2016) on empathic ability. In the first work they assessed if one night of sleep deprivation, compared to one night of sleep spent at home or a period of diurnal wakefulness, results in a reduced emotional empathic response (Guadagni et al. 2014). Emotional empathy was evaluated by a computerized test measuring direct (i.e., explicit evaluation of empathic concern) and indirect (i.e., the observer's reported

physiological arousal) emotional empathy. Sleep-deprived participants were emotionally less empathetic compared to those who had slept, as well as than those retested during the same day, without differences between direct and indirect components of emotional empathy. These results suggest for the first time that a night of sleep loss impairs the ability to share the emotional state of others (Guadagni et al. 2014). In addition, the same group investigated the potential direct relationship between naturally occurring variations in sleep quality and empathic responses of the individuals (Guadagni et al. 2016). In a group of undergraduate students, objective (actigraphy) and subjective (questionnaires and self-reports) sleep measures were collected, to characterize individuals' sleep quality. Participants were then asked to solve a computerized emotional empathy task that provides both direct and indirect emotional empathy measures. The results showed that subjective sleep quality best predicted participants' empathic sensitivity to negative images while they explicitly evaluated the emotions of others. In addition, subjective sleep quality resulted to be the best predictor of participants' arousal state in response to negative images, which is an implicit manifestation of their empathic experience. In both cases, lower subjective sleep quality was associated with lower empathic sensitivity to negative stimuli. Finally, it was found that sleep duration best predicted average empathic responses to stimuli of all valences, with shorter sleep durations associated with lower average empathic responses. Therefore, this study points to a significant relationship between the individuals' quality of sleep and their ability to share the emotions experienced by others (Guadagni et al. 2016). These results are in agreement with studies that showed that poor sleep quality is associated with the reductions in several social and emotive abilities, for instance, the optimism and sociability (Haack and Mullington 2005), and also with lesser emotional intelligence and altered constructive thinking (Killgore et al. 2008). In line with this, the recent study of Brand et al. (2016) explored, in a sample of adolescents, the association between subjective insomnia, emotional competence, and empathy. They observed that higher scores for insomnia correlated with lower scores for some aspects of emotional ability and empathy.

Although few in number, the above described studies are in strict agreement in showing that sleep loss, as well as sleep disturbances or a reduced sleep quality, has clearly negative effects on our ability to correctly process emotional information, to understand the feelings of others, and to be empathic with them.

Altogether, these results may have important clinical and operational implications. Sleep disruption has been shown to impair daytime functioning in several psychiatric disorders such as autism spectrum disorders. In keeping with the evidence that sleep plays a fundamental role in supporting social cognition skills, sleep disturbances may contribute to social cognition disability characterizing children with autism spectrum disorders. Therefore, if this relation between sleep and social behavior is confirmed, interventions to improve sleep in these children may have potential benefits on their social behaviors, with a consequent positive impact on quality of life for the entire family. The operational implications of the same results regard all the professions requiring social interactions and empathic abilities coupled with schedules that curtail sleep.

6.2.4 Sleep, Fear Conditioning, and Threat Generalization

A growing body of literature suggests that sleep plays an essential role also in the acquisition and long-term retention of negative memories such as fear. In the last years, fear conditioning paradigms provided important insights into how fears are learned and extinguished in mammals, thus becoming an important model of fear-related disorders (Milad and Quirk 2012).

In classical paradigms, fear conditioning is obtained by repeatedly pairing a neutral stimulus (e.g., a tone) with a coinciding aversive event (e.g., electric shock), resulting in a fear reaction. Initially the neutral stimulus (unconditioned stimulus, US) does not elicit any emotional reaction, but after this association is formed, the presentation of the neutral stimulus alone (now the conditioned stimulus, CS) become sufficient to evoke a conditioned fear response associated to the anticipation of impending aversive US. As measures of fear response intensity, fear condition paradigms classically include physiological (skin conductance, startle eye-blink electromyography) or behavioral (e.g., freezing) recordings. The CS-US association can also be subjected to extinction, a process that comprises the repeated presentation of the conditioned stimulus (the tone), but now in the absence of the coinciding unconditioned stimulus (the shock), leading to a gradual dissipation of the conditioned fear response (Milad et al. 2006). However, also after extinction, fear responses to the extinguished stimulus can spontaneously reappear with the passage of time (spontaneous recovery), in a new context (renewal) or can be reinstated by repeated spontaneous shock administration (reinstatement), thus suggesting the persistence of the original fear memory trace. According to this, learning that a previously dangerous stimulus no longer signals threat is not merely the erasure of the old fear association, but rather the new acquisition of a coexisting extinction memory mediated by inhibitory mechanisms (Phelps 2004). Fear responses can also be modified by unsafe (e.g., the test environment itself) or safe (e.g., a novel, safe environment) contextual cues, triggering fear reaction or promoting inhibition of the fear response. Moreover, fear learning can be subsequently generalized to other stimuli similar, but not identical to the original specific conditioned stimulus (Lissek et al. 2008).

In the animal model, the crucial role of limbic structures as the amygdala and the hippocampus in standard fear conditioning is now well established. In particular, activity in basal and lateral nuclei of the amygdala has been implicated in fear CS-IU association learning, while the central nucleus of the amygdala is involved in the expression of fear via projections to hypothalamic and brainstem nuclei, which are implicated in the expression of autonomic fear-related responses such as glucocorticoid release, heart rate, blood pressure, and respiratory alterations (Maren 2001; Sotres-Bayon et al. 2006). The hippocampus is crucially involved in detecting and processing contextual relevant information during fear learning; moreover, due to its projections to central amygdala, the hippocampus is also associated with fear expression. Amygdala-hippocampus interplay thus modulates fear response,

enhancing or weakening fear response based on the presence of safe or threatening information cues (Phelps and LeDoux 2005; Fanselow and Dong 2010).

Similarly, two different and mutually opposed networks have been proposed to regulate fear conditioning and fear extinction in humans (Graham and Milad 2011; Milad and Quirk 2012; Milad and Rauch 2012). Specifically, the association of US-CS during conditioning appears to involve basolateral amygdala, whereas extinction learning and recall are known to additionally require the contribution of vmPFC, which exerts an inhibitory modulation on the centromedial nucleus of the amygdala (Milad and Quirk 2002, 2012; Milad et al. 2007; Pitman et al. 2012). Therefore, the activation of the extinction network would inhibit the expression of fear by top-down vmPFC modulation of the amygdala. The human amygdala is involved in affective labeling of stimuli and interacts continuously with the hippocampus in processing emotional aspects of episodic memory (Phelps 2004). The hippocampus plays, in fact, a crucial role in the acquisition of an integrated representation of events and appears implicated in the processing of contextual cues associated to fear learning. In this respect, the hippocampal contribution should consist of successful context recognition for triggering top-down vmPFC inhibition of the amygdala (Pitman et al. 2012).

In the animal model, robust relations between sleep and fear memory have been reported. As an example, total sleep deprivation preceding (Ruskin et al. 2004) or following (Graves et al. 2003; Kumar and Jha 2012) fear conditioning paradigm negatively affects the consolidation of fear memory in the rat. Similarly, in humans a night of sleep has been shown to promote a strengthening of neural, physiological, and behavioral conditioned fear response, paralleled by the activation of basolateral amygdala, compared to sleep deprivation (Menz et al. 2013). In this study, participants performed a fear conditioning paradigm in which they learned to associate different visual stimuli presented in a conditioning context (a picture of a living room) to the administration of a mild electrical shock. Immediately after conditioning, one of these stimuli was presented in association of a new extinction context (a picture of a new context) without shock administration and therefore extinguished. The conditioning phase was followed by one night of regular sleep or a night of total sleep deprivation. During the retest phase, performed after a subsequent recovery night for both groups, individual responses to the administration of previously learned stimuli were tested using explicit memory test of shock expectancy, skin conductance, and functional magnetic resonance imaging (fMRI). Results showed that recall of the previously learned fear was better after the sleep condition compared to sleep deprivation, as reflected in memory performance as well as autonomous skin conductance responses and paralleled by higher activation of the basolateral amygdala. Of particular interest, the amount of time spent in REM sleep was found to be positively correlated with the magnitude of beneficial sleep-dependent consolidation, thus suggesting that sleep, and particularly REM sleep, has a key role in the consolidation of fear conditioning. The authors concluded that sleep preserved fear-related memory, resulting in a better next-day discrimination of fear-related cues (Menz et al. 2013). More recently, the same authors investigated the differential impact of early-night SWS-rich sleep and late-night REM-rich sleep on

the consolidation of conditioned fear and extinction memory (Menz et al. 2016). To this purpose, participants were assigned to four groups subjected to different sleep manipulations. Some participants performed a classical conditioning paradigm with immediate extinction in the evening before they were allowed to sleep for half a night (early sleep group) or had to stay awake until morning (early wake group). Other participants performed both conditioning and extinction after having slept in the first half of the night and were subsequently allowed to go back to sleep (late sleep group) or required to stay awake until morning (late wake group). After a recovery night for all groups, participants underwent the recall session, in which individual responses were assessed using explicit memory test, skin conductance, and fMRI. Results showed that fear memory performance (discrimination between dangerous and safety stimuli) decreased similarly in the early sleep and early wake groups, therefore irrespective of the presence of sleep. Coherently, no behavioral or physiological measures in the early SWS-rich sleep group were indicative of successful fear recall. Conversely, participants who slept in the late REM-rich part of the night showed a better discrimination of fear, at both behavioral and physiological level, in comparison to the late wake group; indeed, participants who stayed awake in the late part of the night showed decreased differentiation between dangerous and safety cues at behavioral as well as autonomic level, thus indicating worse fear memory. Moreover, participants in the REM-rich sleep manipulation showed also better extinction recall performance, while there was no behavioral and autonomic evidence of extinction memory improvements after SWS-rich early sleep. Importantly, in comparison to late REM-rich sleep, subjects who stayed awake in the second part of the night showed a return of fear at both behavioral and autonomic level (indicated by a better discrimination between the previously extinguished and neutral stimuli), paralleled by stronger activations in vmPFC and amygdala. These results indicate that fear and extinction memory performance is not affected by SWS-rich sleep, while beneficiates from REM-rich sleep; on the other hand, lack of REM sleep impairs extinction memory consolidation and promotes a return of fear after extinction. Therefore, the authors suggested that sleep, and particularly REM sleep, could be causal to successful consolidation of dangerous and safety stimuli and contributes independently to effective extinction memory consolidation (Menz et al. 2016).

In fact, sleep has already been suggested to facilitate fear extinction, which is a subsequent new learning of fear inhibition, mediated by top-down PFC inhibition of the amygdala. In the first fear conditioning/extinction study evaluating the role of sleep on extinction memory in humans, Pace-Schott and coworkers (2009) established a fear conditioning by pairing two different color stimuli to the administration of an electric shock, but, immediately after, one of these two associations was extinguished. Extinction recall was subsequently performed, for the sleep group, after a 12-h interval containing a period of nocturnal sleep or after 12 h of continuous wakefulness, for the wake group. Because skin conductance response to the previously extinguished stimulus did not significantly differ between sleep and wake group, this study failed to provide evidence in support of a beneficial role of sleep in the extinction consolidation. However, unlike the wake group, after a night of

normal sleep, participants showed reduced response to the unextinguished stimulus, thus suggesting a role of intervening sleep in the process of generalization of the extinguished memory (Pace-Schott et al. 2009). Subsequent similar protocols from the same group further confirmed a possible link between sleep, retention, and generalization of extinguished memory showing that, after a period of sleep, memory of extinction learning can generalize from an association previously extinguished to another similar but not extinguished association (Pace-Schott et al. 2013, 2014).

In this regard, increasing number of evidence indicates that, among other sleep stages, REM sleep may specifically exert a beneficial role in the processing of extinction memories. The amount of REM sleep obtained following fear extinction was shown to predict a decrease in autonomic arousal based on skin conductance measure (Spoormaker et al. 2010). Accordingly, Spoormarker et al. (2012) aimed at investigating the specific contribution of REM sleep in emotional processing. In this study, participants underwent a fear conditioning/extinction paradigm before sleeping in the laboratory and were then assigned to an experimental or a control group. Participants in the experimental group were subjected to REM sleep deprivation, while the control group received an equal amount of awakenings from NREM sleep stages. Results showed that REM sleep deprivation, in comparison to control multiple NREM awakenings, specifically impaired the consolidation of extinction memory. In addition, an intervening REM period also seems to promote optimal reengagement of ventromedial PFC (vmPFC) involvement during subsequent fear recall, thus ultimately facilitating successful fear extinction (Spoormaker et al. 2012). Spoormaker et al. (2014) have reported that REM sleep amount after fear conditioning negatively correlated with fear responses to the CS the day after. Interestingly, neuroimaging studies in humans showed that the "fear network" areas including the amygdala, vmPFC, insula, thalamus, and dorsal anterior cingulate exhibited increased activation both in fear conditioning/extinction learning and in REM sleep (see also Sect. 6.4). In summary, this evidence strongly supports a specific implication of REM sleep in emotional processing, and in particular in the mechanisms of fear consolidation and extinction, in animals as well as in humans (Dang-Vu et al. 2010). However, a beneficial role of NREM slow-wave sleep in the consolidation of emotional fear learning has been also proposed (Hauner et al. 2013; He et al. 2015).

Collectively, studies of fear learning in humans have alternatively linked sleep to the consolidation of both fear conditioning and fear extinction memory, with mixed results. However, it should be noted that, while in the animal model fear conditioning protocol is a standard, well-established procedure and rapidly induces intense fear responses, considerable methodological differences in human fear conditioning studies (e.g., the type of experimental stimuli, CS-US contingency, immediate versus delay extinction procedure, sleep versus sleep deprivation/wake) could partly underlie the conflicting results among studies.

From a phylogenetic perspective, learning both what to fear and what not to fear are equally important. Despite its fundamental self-preserving nature, the dysfunctional, abnormal persistence of fear conditioning learning could have a role in the pathogenesis and maintenance of anxiety disorders such as post-traumatic stress

disorder (PTSD) or specific phobia. Dysfunctional fear expression in anxiety disorder may indeed result from abnormally strong fear response (Orr et al. 2000; Lissek et al. 2005; Armfield 2006; Mineka and Oehlberg 2008) or alterations of the inhibitory system that normally modulates fear expression (Milad et al. 2006; Craske et al. 2008; Hofmann 2008) (see paragraph 4).

The majority of fear conditioning protocols in humans have indeed focused on the mechanism of extinction learning, due to the relevant clinical implication for exposure therapy in the behavioral treatment of anxiety disorders such as specific phobia, which largely benefit from the formation and subsequent generalization of therapeutic extinction memories (McNally 2007; Craske et al. 2008). In this context, the link between sleep and fear extinction memory has been recently explored also in clinical populations, like spider-fearing women (Pace-Schott et al. 2012; Kleim et al. 2014), showing that, compared to wakefulness, an intervening period of sleep after simulated exposure therapy improved extinction retention and generalization. These preliminary results suggest that post-theraphy sleep may have the potential to enhance the efficacy of the treatment, possibly preventing sensitization to threat and fear generalization (Pace-Schott et al. 2012).

Coherently, sleep disturbances should increase threat perception and promote threat generalization. Contrary to this assumption, Kuriyama et al. (2010) have reported that sleep loss instead resulted in less generalization of negative ratings from an aversive stimulus to a non-aversive stimulus, compared to time spent awake. More recently, Goldstein-Piekarski et al. (2015) investigated the impact of sleep and sleep deprivation on the discrimination of complex social emotion in humans, evaluating both the central and peripheral response to threatening stimuli. To this purpose, participants performed a face recognition task in the fMRI scanner in the morning, after a night of sleep and after a night of total sleep deprivation. During the face recognition task, subjects were asked to classify a set of facial stimuli from not threatening to increasingly threatening. Results showed that the sleep-deprived participants significantly categorized more stimuli as threatening, relative to the rested condition, suggesting that sleep loss could impose a negative bias on the behavioral discrimination of emotional stimuli by enhancing the subjects' tendency to judge affiliative stimuli as threatening. Furthermore, sleep deprivation was associated to alterations in both the functional central and autonomous peripheral (heart rate) activity related to emotional discrimination. Therefore, these results are suggestive of a crucial implication of sleep for an appropriate next-day discrimination of emotional stimuli; conversely, sleep loss could increase threat perception and promote threat generalization in emotional processing. Moreover, results suggest a link between central and peripheral emotional discrimination and the electrophysiology of REM sleep, specifically, the amount of EEG gamma activity during REM sleep in the rested condition (Goldstein-Piekarski et al. 2015).

On the whole, animal and human studies indicate that sleep (particularly REM sleep) is involved in the consolidation of fear memory as well as of fear extinction; yet, the specific direction of sleep-mediated modulation of fear remains to be further clarified. Nevertheless, current evidence collectively suggests an important implication of sleep in emotional memory processing and emotional homeostasis (Walker

and van der Helm 2009). Implicit to the meaning of successful memory consolidation is the crucial ability to next-day discriminate fear and safety relevant information. In this context, sleep may ultimately have the role to promote the adaptive expression of relevant emotions, mediating our ability to discriminate emotional experiences, supporting adequate recognition of salient stimuli, thus the most appropriate response to the environment.

6.3 REM Sleep and Emotions

Since its discovery by Aserinsky and Kleitman in 1953, rapid eye movement (REM) sleep has been closely linked to human emotion. The finding of this unique, paradoxical wake-like sleep stage that is typically associated to reports of emotionally intense, vivid dreams (for a review see Cipolli et al. 2016) has intuitively suggested an intimate association between REM sleep and the emotional domain. Many years of systematic sleep research have investigated the nature of this association, attempting to correlate specific REM features with emotional processing (Walker 2009). Taken as a whole, there are ample evidence now which suggest that the association between REM sleep and emotion is not a phenomenological coincidence but is probably substantial. Here we discuss the role of this unique sleep stage in the offline consolidation of emotional memory and in the modulation of emotional reactivity, with particular regard to the specific physiological REM features that lead to suggest crucial implications with emotional processing.

REM sleep typically emerge approximately 90 min after falling asleep and predominates in the second part of the night, toward the morning. REM sleep remarkably differs from other sleep stages collectively known as NREM sleep. While NREM is characterized by high-amplitude, low-frequency electroencephalographic EEG activity, reflecting a progressively higher degree of synchronization across large neuronal populations, EEG activity during REM sleep is characterized by the presence of low-voltage, mixed frequencies that resemble the activity of quiet wakefulness. Besides rapid eye movements, the hallmark of REM sleep, this stage is characterized by the presence of muscular atonia (Jouvet and Michel 1959) and high-amplitude spiky potentials which propagate from the pontine tegmentum to the lateral geniculate nuclei of the thalamus and the occipital cortex, the so-called ponto-geniculo-occipital (PGO) waves (Jeannerod et al. 1965; Nelson et al. 1983), identified also in humans (Lim et al. 2007). Interestingly, in rodents PGO waves have been linked with emotional memory consolidation (Datta et al. 2004, 2008). REM sleep is also characterized by a predominant theta rhythm, which has been implicated in the integration of information across neocortical networks (Buzsáki 2002).

The beginning of a REM period is accompanied by dramatic alterations in functional brain activity (for more details see Sect. 6.4), with brain areas implicated in memory functions during wake strongly reactivated during this state (Maquet et al. 2000). Such crucial changes are paralleled by significant alterations in brain neurochemistry. In fact, both crucial similarities and differences between the

neuromodulatory state characteristics of REM and wakefulness have been suggested as indicative of a causal role of REM sleep in emotional memory consolidation. Compared to wakefulness, acetylcholine levels in REM sleep are similar or higher. High cholinergic levels could promote synaptic consolidation by supporting plasticity-related activity (Teber et al. 2004) and long-term potentiation (Lopes Aguiar et al. 2008). Conversely, REM sleep is characterized by low noradrenaline levels. In fact, the activity of noradrenergic locus coeruleus neurons increases an animal's ability to pay attention to stimuli in the environment and is strictly related to vigilance performance (Aston-Jones et al. 1994). It has been suggested that during REM sleep, memories within the neocortex are subjected to the plasticity-related cholinergic activity but remain free from arousal-related noradrenergic interference, thus recombining and potentially integrating into existing memory networks (Walker and Stickgold 2010). As proposed, memory reactivation that occurred during REM sleep could promote the integration of recently learned representations into stored superordinate representations (Sterpenich et al. 2014).

Human amygdala and its interplay with the hippocampus has a key role in emotional regulation and in the formation of emotional memories (Strange and Dolan 2006). Stress hormones like cortisol and norepinephrine, released in response to emotional events (Sapolsky et al. 2000), in turn lead to increased activation of the amygdala. Given the strong connection between the amygdala and the hippocampus, amygdala activation by hormones is thought to increase in turn hippocampal activity, thus promoting memory consolidation, particularly for events with emotional valence (McGaugh 2004). Importantly, REM sleep is also associated to a significant increase in cortisol level (Payne and Nadel 2004). In this context, memory consolidation for emotional events may receive an additional contribution from changes in glucocorticoids balance occurring during REM sleep periods.

Converging evidence suggests a role for REM sleep in the offline consolidation of human emotional experiences. First studies on the role of REM sleep in emotional processing used a split-night paradigm (Yaroush et al. 1971). In this procedure, after a learning session, subjects are typically allowed to sleep only in the first 3-h SWS-rich part of the night, thus deprived of late nocturnal sleep, or, conversely, only in the second 3-h part of the night, in which REM predominates, thus deprived of early sleep. In this way, this paradigm is assumed to allow a dissociation of the effects of SWS and REM sleep. In the first split-night study on the role of REM sleep in emotional memory (Wagner et al. 2001), retention of emotional and neutral text was compared over periods of wake, early and late sleep. It has been shown a memory improvement for arousing negative stimuli compared to neutral ones after a late-night REM-rich sleep. Conversely, such beneficial effect on emotional memory retention was not observed after a corresponding wake retention interval or after early-night SWS-rich sleep; the authors therefore concluded that REM sleep can selectively facilitate the consolidation of emotional stimuli (Wagner et al. 2001). Similarly, Groch et al. (2013) investigated the role of early and late sleep on emotional memory retention of emotional or neutral pictures. They reported that compared to early SWS-rich sleep, late-night REM-rich sleep enhanced the retention of negative arousing pictures relative to neutral pictures. More recently, the same

authors confirmed that only late REM-rich sleep enhances the retention of negative relative to neutral stimuli (Groch et al. 2015). However, it was also found that early SWS-rich sleep enhances the retention of the contextual details of the neutral pictures, thus suggesting a differential role of SWS and REM sleep in the consolidation of emotional and neutral stimuli.

Split-night paradigms have demonstrated a better recall of emotional stimuli, compared to neutral stimuli, when the recall session was explicitly performed after a post-learning period containing REM-rich nocturnal sleep. It should, however, be considered that the split-night paradigm, although thought to be less disruptive for the normal sleep architecture in comparison to the selective REM deprivation procedure – which, to a higher extent than SWS deprivation, may include stressful awakenings – is not free from limitations. As an example, testing sessions are typically performed at different time of the day, leading to circadian confounds. Moreover, in the first or second half of the night, a relative predominance of a certain sleep stage on others does not implicate the exclusive presence of this stage, so that, in principle, the split-night design does not allow to selectively refer a specific sleep stage to the observed effect.

The relations between emotional memory and sleep structure have been assessed also by using the napping paradigm. In one of these studies, Nishida et al. (2009) aimed at evaluating the influence of a short nap and a corresponding control wake interval on emotional memory retention. Compared to wake, a nap augmented the consolidation of emotional, but not neutral stimuli. Moreover, it was observed a positive correlation between emotional memory retention and the amount of post-learning REM sleep during the nap. Further, a recent nap study (Gilson et al. 2016) showed that REM density positively correlated with recall performance of sad material in comparison to neutral material. Coherently, Payne et al. (2012) showed a correlation between REM sleep quantity during a nocturnal sleep episode and correct recognition of previously learned emotional stimuli but not with the neutral stimuli. Given the lack of similar correlations for any other sleep stage, results are suggestive of a selective implication of REM sleep in memory processing of emotional stimuli (see also par. 1.4 for a discussion on the contribution of REM sleep to fear memory consolidation and extinction).

In the same direction, a selective sleep stage deprivation paradigm has recently been used to examine the role of SWS and REM sleep in the consolidation and affective evaluation of emotional memories (Wiesner et al. 2015). Here, participants evaluated and learned a set of neutral and negative pictures during the encoding session. Recall session was then performed after a 9-h interval in which participants were subjected to selective SWS or REM sleep deprivation, also including a control wake group who performed the recall after 9 h of wakefulness. Result revealed improvements in the consolidation of the emotional stimuli compared to the neutral ones only in the group that underwent SWS deprivation and conversely had a normal amount of REM sleep.

In accordance with the above results, REM sleep has been proposed as necessary for emotional memory processing. Given the REM sleep-mediated emotional memory enhancement, some authors argued that also the associated emotional charge will

be consolidated along with the memory (Wagner et al. 2002). On the contrary, REM sleep deprivation should inhibit sleep-dependent neural reactivation, which is considered to be essential for memory consolidation processes, thus impairing the long-term retention of a memory and of its emotional tone (Wagner et al. 2006). As per such assumption, and considering the facilitatory role of sleep in emotional memory consolidation, the use of sleep deprivation as a potential therapeutic tool to prevent long-term retention of traumatic events has been also suggested (Wagner et al. 2006).

Although results suggest that during REM sleep an active consolidation process of emotional experiences takes place, nevertheless the direction and specificity of the effects of REM sleep in emotional memory processing is still debatable. In fact, alternative to the previous hypothesis, the "sleep to remember, sleep to forget" model (Walker and van der Helm 2009) argues that the unique neurobiological state of REM sleep could act to de-potentiate, rather than strengthen, the emotional charge of a memory. In particular, the reprocessing of emotional memories would be supported by the reactivation during REM sleep of specific brain areas implicated in memory function in wake, such as the amygdala and the hippocampus (see Sect. 6.3 of this chapter). Further suggestive of a causal role of sleep in memory processing, theta oscillations, which dominates REM stage, are supposed to be implicated in the consolidation and integration of different aspects of memory representations (Buzsáki 2002). In this respect, recall of dreaming experience is associated to higher theta oscillations only upon awakening from REM sleep (Marzano et al. 2011; Scarpelli et al. 2015). Crucially, unlike emotional memory formation during wakefulness, these memory-relevant processes occur in a brain state characterized by dramatically reduced aminergic, particularly noradrenergic, neurochemical concentration. Thus, within this unique *scenario*, the activation of the amygdala-hippocampal network is proposed to facilitate the long-term retention of the informational, salient elements of an emotional experience ("sleep to remember"). Contextually, the suppressed adrenergic activity during REM sleep, which in wake is associated to arousal, is supposed to separate from the emotional memory the visceral, autonomic charge originally associated to emotional experiences and gradually dissipate it ("sleep to forget"). In this way, according to the authors, REM sleep could be viewed as an "overnight therapy" which adaptively protects the salient aspects of a memory, obliterating at the same time the associated emotional tone (Goldstein and Walker 2014).

In this respect, although a negative correlation between REM sleep and subsequent attenuation of negative emotional response to affective stimuli has been reported (Baran et al. 2012), there are also evidence suggesting a sleep-dependent decrease in both subjective emotional arousal and autonomic response to negative stimuli compared to a comparable wake interval in humans. Therefore, these results support the "sleep to forget" part of the hypothesis. In this direction, van der Helm et al. investigated the role of sleep, with particular regard to REM sleep, on emotional processing (van der Helm et al. 2011). Participants performed 2 repeated fMRI tests in which they were asked to view 150 affective pictures and rate the subjective emotional intensity associated to each picture. The second fMRI session was performed after a 12-h interval of wake or after an equal interval containing a

night of sleep. Results indicated an overnight decrease in amygdala responsiveness at retest paralleled by a corresponding behavioral decrease in emotional reactivity to the emotional stimuli. Emotional intense ratings indeed significantly decreased in the sleep group, with a progressive increase in neutral subjective ratings. Interestingly, this study also provided insight into a link between REM sleep physiology and emotional processing, showing a relation between decreased reactivity at both cerebral and behavioral level and the extent of reduced EEG gamma activity during REM sleep, which is considered a marker of reduced central adrenergic activity (Maloney et al. 1997; Cape and Jones 1998).

Moreover, according to this theory and opposite to the Wagner and colleagues' hypothesis (Wagner et al. 2006), sleep deprivation should block the beneficial overnight emotional depotentiation. Neuroimaging (see the next section) and behavioral studies seem to support to this prediction. In fact, sleep loss is associated to a reduced functional connectivity between the amygdala and the vmPFC and therefore a lack of top-down limbic control by the PFC, resulting in an amplified limbic activity in response to negative emotional stimuli (Yoo et al. 2007). The hyperlimbic activation observed after sleep deprivation could also affect the assessment of emotional stimuli, leading to an increased negative evaluation of these stimuli (Yoo et al. 2007) or even to an increased tendency to judge neutral stimuli as more negative (Tempesta et al. 2010). Moreover, such amplified reactivity of the amygdala after sleep loss in response to negative pictures could also explain the specific resistance of unpleasant stimuli to the detrimental effect of sleep loss on memory, as assessed by a recognition memory task (Tempesta et al. 2016). Thus, according to the implications of the theory, REM sleep may represent a preventive therapeutic measure for emotional brain homeostasis, preparing the organism for next-day emotional functioning, priming brain areas to appropriately react to emotional experiences, and thus ultimately promoting an adaptively accurate discrimination of the emotional stimuli (Goldstein and Walker 2014).

However, it should be noted that the available findings on the specific involvement of REM sleep in offline emotional memory consolidation or emotional reactivity are in part contradictory. In fact, in other selective REM deprivation paradigms, a specific beneficial role of REM sleep in emotional memory processing was not observed (Morgenthaler et al. 2014; Kaida et al. 2015). Furthermore, in a recent daytime nap study, it has been shown that a brief sleep period improves memory consolidation of both emotional and neutral material, regardless of the presence of REM sleep (Cellini et al. 2016). As far as emotional reactivity is concerned, the above reported study by Baran and colleagues (2012) showed that a longer time in REM sleep is related to a protection – more than a depotentiation – of emotional reactivity. As suggested by the authors, although the reduction of emotional reactivity to new stimuli would positively contribute to mental health, in an evolutionary perspective, the preservation of salience might have been of great advantage to survival. Indeed, by maintaining the negative tone together with the strengthened memory trace, the individual will not only remember the emotional event but also the degree of threat associated with it (Baran et al. 2012). Further, in the study of Groch and coworkers (2013), the improvement of emotional memory

dependent on REM sleep was not accompanied by a next-day significant decrease in subjective emotional ratings indicative of a beneficial role of REM on emotional reactivity. Therefore, the lack of significant decreases in emotional evaluation after both early SWS-rich and late REM-rich sleep suggests a protective role of sleep per se also on the affective tone associated to emotional memories, which is obtained along with their sleep-dependent processing and consolidation. Moreover, as a further contribution to the assumption that REM sleep may strengthen the emotional charge of a memory, Lara-Carrasco and colleagues (2009) observed after partial REM sleep deprivation, an increased emotional adaptation to negative stimuli with a corresponding decrease in subjective arousal ratings for those stimuli, in comparison to subjects that underwent undisturbed nocturnal sleep and therefore had more REM sleep. Therefore, as suggested in this study, REM sleep could even enhance emotional reactivity to negative stimuli.

In conclusion, the large overlapping between the neuroanatomophysiology of REM sleep and emotional processing continues to appear not coincidental to many researchers. On the whole, increasing results observed with different experimental paradigms suggest a critical implication of REM sleep in overnight emotional modulation, although the direction of this effect is not established. Indeed, there are now two opposite theories regarding the specific modulation by REM sleep of the salience associated to memory traces, something that ultimately makes our episodic memories, emotional memories. According to these different assumptions, REM sleep could therefore facilitate the retention of the emotional memory charge (Wagner et al. 2006) or, conversely, de-potentiate the visceral tone associated to a memory (Walker and van der Helm 2009) with some evidence existing in support or against both models, showing enhanced (Wagner et al. 2002; Lara-Carrasco et al. 2009; Baran et al. 2012) or diminished (van der Helm et al. 2011) REM-related emotional reactivity, as well as no effect specifically associated to REM sleep (Groch et al. 2013; Wiesner et al. 2015). When trying to account for such discrepancies, it should be considered that the remarkable variety of the experimental paradigms, each one with specific limitations, often makes difficult a direct comparison of the results, so that such methodological differences may have a substantial role in the interpretation of the contrasting results. Further, a potential limitation in studies on sleep and emotions lies in the experimental task used, which typically involve the administration of stimuli (such as emotional pictures) that may be not sufficient to elicit strong emotional reactions. This could be even more relevant considering the clinical implications of both models for the processing of traumatic experiences, which are – at least quantitatively – different from standardized negative emotional stimuli and far from being elicited by the experimental administration of emotionally arousing pictures. Further studies are required in order to better elucidate the sleep and emotions relationship, including more ecological experimental tasks and limiting other possible multiple confounding factors.

6.4 Sleep and Emotions: Insights into the Brain Mechanisms by Neuroimaging Studies

The introduction of neuroimaging techniques, particularly positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), marked the beginning of a new era in the neurosciences. Such techniques, by detecting increases in regional cerebral blood flow or blood-oxygen level-dependent (BOLD) signal as markers of neuronal activity, allowed to explore functional brain processes in the intact human brain and shed light into the functional neuroanatomy of a variety of processes, including human emotion. Examining emotion-related activity in human brain, neuroimaging allows to identify brain areas specifically associated to emotional states, obtaining therefore a direct measure of emotions at their source. Importantly, neuroimaging insights into the neural correlates of emotional processing have corroborated and substantiated behavioral results as well prior investigations based on animal and brain lesion model.

Functional neuroimaging techniques have contributed to identify several brain areas involved in human emotional processing. Essential, in this human emotional network, is the hippocampal-amygdala-medial prefrontal cortex network. Amygdala has a key role in emotional processing. The influence of emotional arousal on memory specifically involves the activation of the amygdala. Indeed, during emotional arousing events, the crucial interaction between stress hormones and amygdala represents an endogenous memory-modulating system which regulates memory storage processes in other emotional relevant brain regions. The amygdala has been implicated in emotional responsiveness to aversive stimuli also in humans (for a review, Cahill and McGaugh 1998). The activation of this structure is indeed closely linked to emotional intensity of the stimulus and has been shown to correlate with subjective emotional arousal (Phan et al. 2003) and autonomic arousal skin conductance response (Williams et al. 2001). Importantly, amygdala activation also results in behavioral changes, as both PET and fMRI studies showed that amygdala activity induced by emotional stimuli at encoding highly correlates with memory at subsequent recall, suggesting a clear implication of the amygdala in modulating hippocampal memory consolidation (for a review, Phelps 2004). Indeed, converging evidence support the idea that amygdala activation has a crucial role also in promoting subsequent memory consolidation processes, modulating striatal, prefrontal, and particularly hippocampal activity, which is critically implicated in memory storage (for a review, McGaugh 2004). In this emotional network, the medial prefrontal cortex (mPFC) has been shown to have a crucial role in emotional processing; importantly, mPFC, via strong inhibitory top-down projections, is proposed to exert a modulatory impact on amygdala activation, thus resulting in contextually appropriated emotional responses (Davidson 2002; Sotres-Bayon et al. 2004).

In recent years, the introduction of neuroimaging techniques in sleep research is progressively providing important insights into a possible implication of human sleep in memory processing and emotional reactivity. PET studies showed a whole-brain metabolism decline from waking to NREM sleep, while global brain metabolism levels are comparable between REM sleep and wakefulness (Maquet et al. 2000; Nofzinger et al. 2002). Importantly, neuroimaging studies revealed that brain areas involved in emotional memory processing during wakefulness are strongly reactivated during sleep (Nir and Tononi 2010). In fact, the earlier PET studies showed specific neuronal network activity throughout REM sleep within the amygdala, entorhinal cortex, and anterior cingulate (Hong et al. 1995; Maquet et al. 1996; Braun et al. 1997, 1998; Nofzinger et al. 1997; Buchsbaum et al. 2001; Peigneux et al. 2001). The higher activation during REM sleep of emotion-related cerebral areas has been confirmed by the few available fMRI studies (Miyauchi et al. 2009; Dang-Vu et al. 2010). Moreover, transient co-activation of the amygdala, hippocampus, and cingulate has been reported by an EEG-fMRI co-registration study (Wehrle et al. 2007), suggesting that REM sleep could have a fundamental implication in emotional memory reprocessing.

Importantly, Yoo and coworkers (2007), using fMRI, aimed at investigating the impact of sleep and sleep loss on the emotional memory network. In this study, participants were subjected to a night of normal sleep or total sleep deprivation prior to an fMRI scanning session in which emotional pictures ranging from neutral to increasingly negative were administered. In response to increasingly negative emotional stimuli, participants that were sleep-deprived exhibited a significantly greater amygdala activation compared to the sleep group. Moreover, sleep-deprived subjects also showed an increase in the volumetric extent of the amygdala activation in response to negative stimuli. Interestingly, an altered pattern of functional connectivity was also reported. Specifically, sleep deprivation was associated to a loss of functional connectivity between amygdala and mPFC, along with an increased connectivity between amygdala and autonomic-activating brainstem areas. Conversely, after a night of sleep, a significant stronger amygdala-mPFC functional connectivity was observed (Yoo et al. 2007). Therefore, these results indicate that a night of sleep deprivation is associated to an amplified limbic response to negative stimuli. This activity pattern suggests a failure of top-down prefrontal control over emotional areas.

Moreover, the effects of sleep restriction on emotional reactivity to emotional faces showing happy, fearful, and neutral expression have also been investigated (Motomura et al. 2013). In this study, participants underwent a sleep restriction paradigm in which time in bed was limited to 4 h a day for a period of 5 days, or conversely they were allowed to regularly sleep at home. Sleep restriction was associated to a greater amygdala activation for negative stimuli, along with a reduced amygdala-anterior cingulate cortex connectivity. This result again suggests a detrimental role of sleep loss on emotional regulation. However, sleep loss could not be exclusively associated with enhanced reactivity to negative stimuli (Yoo et al. 2007; Franzen et al. 2009), but rather to a more generic lability in emotional regulation. Indeed, Gujar and coworkers observed, after a night of total sleep deprivation, higher

activity in mesolimbic regions in response to pleasure-evoking stimuli with a reduced connectivity in medial- and orbitofrontal areas (Gujar et al. 2011).

Therefore, sleep deprivation could promote a generalized affective imbalance leading to an amplified reactivity across different affective valence, including negative as well pleasant experiences. In summary, these evidences confirm the importance of sleep for brain emotional homeostasis, in order to preserve an effective functional PFC-limbic connectivity and thus to restore an appropriate next-day emotional reactivity (Yoo et al. 2007; Walker 2009).

In order to assess a specific implication of REM sleep in emotional processing, Rosales-Lagarde and colleagues (2012) evaluated the effect of selective REM sleep deprivation on emotional responses to threat-related visual stimuli. To this purpose, subjects underwent fMRI scan twice, after a baseline night and after one night of either selective REM sleep deprivation or a control night in which participants were subjected to an equal amount of NREM sleep interruptions. During the emotional reactivity task, participants viewed threating or not threating pictures, and they were asked to imagine themselves as a part of the scene and rapidly react to the situation by choosing to defending themselves or not. Emotional reactivity, behaviorally assessed as the number of defensive choices against threatening scenes, resulted enhanced after selective REM deprivation but not after comparable NREM interruptions, relative to the baseline night. Moreover, at the neural level, results showed an overall decrease of activation in areas involved in emotional processing, particularly occipital and temporal areas and ventrolateral prefrontal cortex in the control NREM group, while the activity in these areas was similar or higher compared to baseline in the REM deprivation group. This result seems to indicate that lack of REM sleep leads to enhanced emotional next-day reactivity to threats, supporting, therefore, the role of this sleep stage in emotional homeostasis (Walker and van der Helm 2009). Indeed, fMRI studies indicated that sleep affects emotional memory network, leading to post-sleep increased activity in amygdala and ventromedial PFC (vmPFC) and to strengthened connectivity between the amygdala and both vmPFC and hippocampus during successful retrieval of negative objects (Payne and Kensinger 2011). This result could be relevant not only for adequate emotional reactivity but also for emotional memories encoding and consolidation processes.

In fact, converging evidence suggest that sleep could also have a direct implication in all stages of emotional memory formation. In this regard, the impact of sleep loss on the neural dynamics associated with emotional memory encoding and consolidation can be successfully elucidated using sleep deprivation paradigms that include event-related fMRI acquisition in conjunction with behavioral measures. In a behavioral-fMRI study, Sterpenich et al. (2007) examined the impact of sleep and sleep deprivation on emotional memory consolidation. Participants were subjected to a first fMRI scanning session in which they encoded a set of neutral or emotional pictorial stimuli. In the first post-encoding night, subjects were allowed to regularly sleep at home, or, conversely, they were sleep deprived. A second fMRI scanning session was performed 3 days later for both groups, during the recall session. During recall, participants made recognition memory judgments about previously learned pictures and new pictures. Behavioral results here showed that

recollection of neutral or positive stimuli, but not negative stimuli, was significantly deteriorated after sleep deprivation. At the neural level, compared to neutral items, recollection of emotional stimuli was associated with increased responses in the hippocampus and several cortical areas, including the mPFC, in subjects that were allowed to sleep the first night post-encoding session, relative to sleep-deprived participants. Furthermore, regarding the recollection of negative stimuli, while the sleep group elicited a consistent hippocampo-neocortical activity pattern, an alternate amygdalo-neocortical network was recruited after sleep deprivation, compared to the sleep group. The authors suggest that such activity pattern in sleep-deprived subjects could represent an adaptive strategy to keep track of salient, potentially dangerous environmental features, despite the detrimental effects of sleep deprivation on cognition (Sterpenich et al. 2007). In a subsequent fMRI study, the same authors (Sterpenich et al. 2009) assessed the impact of sleep in the first post-encoding night on the recall of remote emotional memory. Participants were therefore scanned during a delayed second retest session, performed 6 months later, in which they were asked to make a recognition memory judgment about formerly learned pictures mixed with additional new ones. At the behavioral level, results showed that recollection rate decreases over time, but the emotional items remained still better remembered than the neutral ones, 3 days as well 6 months later. Although no significant behavioral differences in the recall session between the two groups were observed, after 6 months the recollection elicited significantly higher responses in subjects that were allowed to sleep, compared to the sleep-deprived ones, in the vmPFC and precuneus, as in the amygdala and occipital cortex. A stronger connectivity was also found between the vmPFC and precuneus, amygdala and occipital cortex, as well as amygdala and vmPFC (Sterpenich et al. 2009). Thus, sleep during the first post-encoding night can exert a significant impact on the long-term consolidation of memories at the system level. These evidences suggest that the offline processing of emotional memory during the first night is linked to a progressive consolidation process, resulting in strengthening of connections among those areas that are subsequently recruited during memory recall.

Nevertheless, the fact that the same brain areas involved in fear learning and emotional processing during wake are selectively reactivated during REM sleep (e.g., Nir and Tononi 2010) encourages to explore more directly the functional implications of this neuro-anatomo-physiological overlapping. In a recent study, Sterpenich et al. (2014) aimed at investigating the role of specific memory reactivation during REM sleep on subsequent memory performance and brain activations. In this study, participants underwent fMRI scanning both at encoding session, in which they rated emotional negative and neutral face stimuli, and at recall session, when they underwent a recognition task. During the encoding, two distinct auditory cues were associated to the administration of emotional or neutral faces. During the subsequent post-encoding night, the same auditory cues previously associated to the stimuli were again delivered during periods of phasic REM or during stage 2 NREM, while some participants were administered two new sounds, during phasic REM sleep, or slept undisturbed. Results indicated that the administration of auditory cues during REM periods in post-encoding night is capable of

inducing significant changes in brain activations and next-day memory performance. Specifically, the association between visual and auditory features of a memory was effectively strengthened by subsequent memory reactivations experimentally induced by the presentation of cues during REM sleep, as suggested by enhanced activity in the areas recruited during encoding. Notably, at the behavioral level, the administration of auditory cues during REM sleep, in comparison to cues delivered during NREM and unstimulated sleep, resulted in both correct and incorrect recollection enhancement, at memory retest. In other words, cues delivered during REM sleep selectively enhanced subsequent correct face recognition, but also false recognition, when participants were asked to make recognition judgments at retrieval. As argued by Sterpenich and coworkers, therefore, memory reactivation during REM could enhance brain responses at retrieval, indicating a process of integration of new memories within cortical circuits. Moreover, behavioral evidence indicates that REM sleep promotes a process of feature extraction of a memory and the subsequent association with other semantically related representations, leading to an identification bias of new faces as previously learned. Therefore, REM sleep could have an important role for the progressive integration of new episodic memories into existing representation stored in cortical networks (Sterpenich et al. 2014).

In conclusion, although at an initial stage, the introduction of functional neuroimaging techniques in the study of the relations between sleep and emotions is progressively contributing to disclose a protective role of sleep on human emotional homeostasis and emotional regulation. Further, sleep seems to be critically involved also in the ability to form and retain emotional episodic memory. Finally, some evidence suggests that particularly REM sleep, a period characterized by a high activity in brain regions involved in emotional memory processing, could be implicated in the processing of emotional information.

6.5 Sleep and Emotions in Psychiatric Disorders

The importance of understanding the links between sleep and emotion is apparent in light of the robust scientific evidence demonstrating associations between sleep and affective or anxiety disorders (Dahl and Harvey 2007; Baglioni et al. 2010; Gregory and Sadeh 2012). It's not a coincidence if, in the Diagnostic and Statistical Manual of Mental Disorders-V (DSM-V) and in the International Classification of Diseases (ICD-10), disturbed sleep is a key symptom of many psychiatric disorders. For example, poor sleep is a pervasive problem for patients suffering from depression or post-traumatic stress disorder (PTSD). Epidemiological studies demonstrated that sleep disturbances such as insomnia are found in up to 80% of the individuals with major depressive disorder (Selvi et al. 2010), and the rate rises to nearly 90% when an anxiety disorder is present concomitantly (Ohayon et al. 2000).

Insomnia is one of the most prevalent sleep disorders and has a significant impact on individual's health. This disorder is characterized by difficulties initiating or maintaining sleep or non-restorative sleep, accompanied by significant daytime

impairments (Feige et al. 2013). Several studies found a relationship between poor sleep quality in insomnia and emotional functioning. For example, it has been recently shown that insomnia affects the subjective ratings of emotional stimuli (Kyle et al. 2014). Moreover, functional neuroimaging studies reported that subjects with insomnia show an increased amygdala activation to insomnia-related stimuli compared to healthy subjects (Baglioni et al. 2014). In line with these data, it has been also observed in participants reporting poor sleep a significant association between amygdala reactivity and levels of depression and perceived stress (Prather et al. 2013).

These data suggest that sleep quality is an important behavioral modulator of the neural correlates of mood and emotional processing, underscoring the bidirectional relationship between poor sleep quality and affective or anxiety disorders. Therefore, as much mood and anxiety disturbances may be attributable to the emotional instability due to sleep loss, as poor sleep quality may be attributable to the mood and anxiety disturbances.

6.5.1 Major Depressive Disorder (MMD)

Major depressive disorder (MDD) is the most prevalent mood disorder, characterized by a prolonged dysphoric mood state usually accompanied by debilitating emotional, behavioral, cognitive, and physical symptoms. One of the most consistent symptoms associated with major depressive disorder is sleep disturbance (Peeters et al. 2006; Peterson and Benca 2008; Baglioni et al. 2011). Whereas about 80% of the patients complains of insomnia, 15–35% suffers from hypersomnia (Hawkins et al. 1985; Armitage 2000).

Typical symptoms of patients with MDD are difficulty getting to sleep, frequent awakenings during the night, early morning awakening, or nonrestorative sleep. Polysomnographic studies in adult depression confirm a clear pattern of altered sleep, characterized by a shortened REM latency, a prolongation of the first REM period, an increased number of eye movements (REM density) during REM sleep, and an attenuation of slow-wave sleep, particularly early in the night (Pillai et al. 2011; Baglioni et al. 2016). These data clearly indicate that sleep and depression are closely intertwined.

Such a strict relation is also supported by a bulk of data on the effects of sleep loss on mood. The negative consequences of lower quantities of sleep on mood have been repeatedly observed (Pilcher and Huffcutt 1996; De Valck and Cluydts 2001; Dahl and Lewin 2002; Oginska and Pokorski 2006). For example, De Valck and Cluydts (2001), comparing in young adults the depressed mood the day after 4.5 h or 7.5 h of sleep, observed that the subjects who slept less reported higher depressed mood compared with the group who slept longer. Accordingly, a meta-analysis indicated that partial and total sleep deprivation exert their largest effects on

mood, more than on performance (Pilcher and Huffcutt 1996). These findings demonstrate that a poor night's sleep have profoundly negative effects on depressed mood.

Several studies have identified alterations in functional brain activity during sleep in subjects with mood disorders in comorbidity with sleep disturbances (Germain et al. 2004; Nofzinger et al. 2004). During NREM sleep, the typical decrease of metabolic activity in the frontal, temporal, and parietal cortex compared with waking levels is smaller in depressed compared to healthy subjects (Ho et al. 1996; Peterson and Benca 2008; Nofzinger et al. 2004). Instead, during REM sleep an activation in the anterior paralimbic structures relative to waking was observed both in healthy and in depressed subjects, even if the spatial extent of this activation was greater in depressed patients (Nofzinger et al. 2004). In addition, during REM sleep patients showed a greater activation in prefrontal areas. These evidence suggest that the accentuated activation of paralimbic and prefrontal circuits during REM sleep could reflect the emotional dysregulation typical of depression disorder (Davidson et al. 2002; Tsuno et al. 2005). In these subjects an analogous dysregulation in the activation of the amygdala has been shown to affect the assessment of emotional, especially negative, visual stimuli (Jaworska et al. 2015). Moreover, in MDD patients a non-specific amygdala reactivity has been shown that does not discriminate between negative, neutral, and positive images (Ritchey et al. 2011).

Similarly, in patients with insomnia disorder compared to healthy good sleepers, heightened amygdala responses to insomnia-related pictures eliciting negative emotions have been observed (Baglioni et al. 2014). Such amygdala hyper-activation in response to negative emotional stimuli resulted to negatively correlate with total sleep time, sleep efficiency, slow-wave sleep, and REM sleep, further supporting a key role of sleep for emotional balance (Baglioni et al. 2014).

While the association between sleep disturbances and depression seems well clarified, the debate about the cause and effect relationship is still open. Even though insomnia can be an independent diagnostic entity, it has been pointed out that often this disturbance precedes the onset of mental disturbances such as major depression (Livingston et al. 1993; Weissman et al. 1997; Breslau et al. 1997; Chang et al. 1997; Riemann and Voderholzer 2003; Baglioni et al. 2010, 2011). In fact, several longitudinal studies have shown that sleep disturbances act as risk factors for depression (e.g., Eaton et al. 1995; Cole and Dendukuri 2003; Taylor et al. 2003; Buysse et al. 2008). Non-depressed people with insomnia have a twofold risk to develop depression, compared to people with no sleep difficulties (Baglioni et al. 2011). Coherently, it has been found that from 17% to 50% of subjects with insomnia, symptoms lasting 2 weeks or longer showed the development of a major depressive episode in a later interview (Buysse et al. 2008).

Whether sleep disorders trigger depression symptoms, their treatment could be important because it might influence the onset of depression. However, insomnia does not always precede depression. Other longitudinal studies have indeed found evidence for depression as a risk factor for developing insomnia (e.g., Jansson and Linton 2006; Morphy et al. 2007).

In conclusion, even if there is ample evidence about the reciprocal relationships between sleep disturbances and depression, the direction of this relation is still a matter of debate. However, the fact that emotion regulation is altered in insomnia subjects could explain why insomnia leads to depression (Koffel and Watson 2009; Baglioni et al. 2010). An altered pattern of brain activation during sleep (such as the increased activation of paralimbic and prefrontal circuits during REM sleep) may lead to alterations in emotional reactivity and then to greater likelihood of developing depression.

6.5.2 Anxiety Disorders

Anxiety disorders constitute the most frequent mental disorder in the general population yet often go undiagnosed. The overall lifetime prevalence of anxiety disorders is 24.9% (Bruce et al. 2005). Most anxiety disorders have a strong relationship with sleep problems (Ramsawh et al. 2009). Among anxiety disorders, the generalized anxiety disorder and social phobia had the strongest relationships with global sleep quality. Similarly, in a study on the prevalence of sleep-related problems in youth with anxiety disorders, one or more sleep-related problem was reported in 88% of the participants (Alfano et al. 2007).

Subjective complaints of difficulty falling asleep and frequent night-time awakening are the most common complaints in people with anxiety disorders. Objective polysomnographic data demonstrated a disrupted sleep continuity with significant reduction of total sleep time and sleep efficiency. In addition, sleep latency was prolonged, while NREM sleep amount was reduced (Benca et al. 1992; Papadimitriou and Linkowski 2005).

The clinical picture for sleep changes in anxiety disorders is similarly to that described for depression. Insomnia, frequently associated with the anxiety disorders, may precede or follow the onset of a comorbid anxiety disorder (Ohayon and Roth 2003; Johnson et al. 2006; Jansson-Frojmark and Lindblom 2008).

While there is less evidence compared to depression for the relationship between sleep disturbance and anxiety, some studies have found that chronic insomnia predict the first onset of anxiety disorders (Jansson-Frojmark and Lindblom 2008; Jackson et al. 2014). Ohayon and Roth (2003) showed that anxiety disorder appears before insomnia in 43% of cases, but in 18% of cases insomnia appears before the anxiety disorder.

Anxiety may also be a risk factor for future insomnia (e.g., Ohayon and Roth 2003; Jansson and Linton 2006; Morphy et al. 2007). In fact, it has been observed that high anxiety increased the risk of developing insomnia by more than three times (Jansson and Linton 2006).

Anxious individuals seem to show emotional hyper-reactivity, manifested as relatively intense and frequent negative emotional responses to perceived threat. Consequently, since anxious individuals provide exaggerated negative emotional

response to threatening scenes, they experience frequent and intense negative emotions (Carthy et al. 2010).

Emotion dysregulation is thought to be a core feature of anxiety disorders (e.g., Mennin et al. 2007). In fact these patients have an exaggerated negative emotional reactivity (Goldin et al. 2009; Mennin et al. 2005), an impaired facial emotion recognition (Melfsen and Florin 2002), and react with a higher increase of heart rate to threatening stimuli or situations, compared with non-anxious controls (e.g., Beidel et al. 1985).

Additionally, trait anxiety is associated with reduced prefrontal-amygdala connectivity involved in emotional modulation (see Greening and Mitchell 2015). Interestingly, this lack of prefrontal-amygdala functional connectivity has been found also after sleep loss (Yoo et al. 2007). This evidence, emphasizing the importance of the interactions between these brain structures in modulating anxiety, may also suggest an additional role of sleep in emotional modulation. However, to date no studies have investigated the presence of prefrontal-amygdala connectivity also in anxiety disorders with sleep disturbances. This could represent an important direction for further research.

6.5.3 Post-traumatic Stress Disorder (PTSD)

PTSD is another major psychiatric disorder with poor sleep being one of its principal symptoms (see Germain 2013). In fact, in the 5th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-V; APA 2013), sleep disorders are included among the criteria for PTSD. These include re-experiences of traumatic symptoms (nightmares, criteria B) as well as alterations in arousal and reactivity (sleep disturbance, criteria E).

We have recently found that the exposure to a traumatic disaster was related to a significant deterioration of sleep quality and an increased occurrence of disturbing nocturnal behaviors, even 2 years after the event (Tempesta et al. 2013). Indeed, sleep disturbances were the prevalent symptoms among persons who survived the 1995 Hanshin earthquake in Japan (Kato et al. 1996) and among survivors of the Holocaust (Kuch and Cox 1992).

The most commonly reported complaints of PTSD patients are difficulties in falling asleep, regular awakenings (with difficulties in falling back to sleep), reduced sleep duration, restless sleep, fatigue, and, above all, anguished nightmares and anxiety dreams. The 44–90% of combat veterans with PTSD reported some sleep disturbances (Mellman et al. 1995; Neylan et al. 1998), and 52–87% reported having persistent nightmares (Inman et al. 1990). The nightmares are the most constant evidence in the majority of studies that have investigated sleep in PTSD patients (Lichstein and Morin 2000; Ohayon and Shapiro 2000), so that they are considered a core symptom of PTSD (Spoormaker and Montgomery 2008).

Meta-analytic review (Kobayashi et al. 2007) of 20 polysomnographic studies comparing sleep in people with and without PTSD showed that PTSD patients had

more stage 1 sleep, less slow-wave sleep, and greater REM density compared to people without PTSD. Conversely, reduction or fragmentation of REM sleep has been observed in the acute aftermath of trauma exposure and in symptomatic populations within several years of the onset of PTSD (Mellman et al. 2002; Redline et al. 2004; Habukawa et al. 2007).

According to the Walker and van der Helm model (2009), REM sleep could play an important role in PTSD development. In fact, REM sleep would be important not only for the persistence, in memory, of the emotional experience, but also for the depotentiation of the affective tone associated with the experience (Walker and van der Helm 2009). Therefore, when during the night after the traumatic event, sleep is disrupted, the process of separating the affective tone from the emotional experience cannot be accomplished; consequently, the subjects continue to display hyperarousal reactions to associated trauma cues (Harvey et al. 2003; Pole 2007) (for a more detailed explanation of the model, see Sect. 6.4).

Conversely, on the basis of the evidence that REM sleep following learning supports emotional memory consolidation (Wagner et al. 2001), Wagner and colleagues (2006; for more details, see Sect. 6.4) argue that after traumatic events, REM sleep may contribute to the development of haunting emotional memories, which can resist forgetting over long time periods and, in extreme cases, eventually manifest themselves in PTSD. From this perspective, these authors suggest the use of sleep deprivation in the immediate aftermath of traumatic events as a possible therapeutic measure to prevent a long-term persistence of these events in memory or at least to partly counteract the development of PTSD (Wagner et al. 2006).

In summary, REM sleep has been suggested to be crucial for the traumatic memory retention; however, regarding the affective tone associated to a traumatic memory, according to different views, REM sleep could promote its strengthening (Wagner et al. 2006) or, conversely, could dissipate (Walker and van der Helm 2009) its emotional charge.

Over the past several years, structural neuroimaging studies provided evidence that PTSD patients exhibit structural abnormalities in brain regions that are involved in stress regulation and fear responses, such as the amygdala, anterior cingulate cortex, and ventromedial prefrontal cortex (Shin et al. 2004; Driessen et al. 2004). Functional neuroimaging studies have also reported an increased activation of limbic structures, such as the insula and amygdala, during emotional tasks in PTSD individuals compared to healthy subjects (e.g., Mazza et al. 2013). Other studies have also demonstrated that patients with PTSD show reduced neural activity in the medial prefrontal cortex (mPFC) and increased activity in the amygdala during exposure to negative stimuli (Liberzon et al. 1999; Shin et al. 2004; Ganzel et al. 2008). In a study investigating the effective connectivity between the specific brain areas activated during emotional processing of negative stimuli, we observed that the higher reactivity to negative emotional stimuli in limbic brain regions is paralleled by a modification of the fronto-limbic functional connectivity in PTSD subjects (Mazza et al. 2013). Such dysfunction, which leads to a reduced cortical control of limbic areas that, in turn, result hyperactivated, may be the substrate of the peculiar

emotional symptoms of PTSD. Among these symptoms, individuals with PTSD experience feelings of detachment from others, disinterest in once pleasurable activities, and a restricted range of emotions, a class of problems referred to as emotional numbing. This may lead to a reduction of emotional ability and affective inclination for others and, generally, to a decrease of social interactions (Litz and Gray 2002).

Moreover, there is evidence that PTSD patients have difficulty to experience intimacy and tenderness and feel at times emotional disconnected from other people (Porto et al. 2009). We have reported that PTSD is characterized by impairments in emotional empathy, accompanied by a reduced neural activity in the left insula and the left inferior frontal gyrus (Mazza et al. 2015). Interestingly, the functional connectivity of the cortical areas involved in empathic behavior is also altered in PTSD. In these patients, increased activity in limbic regions such as the insula and the amygdala modulates activity in the frontal cortex while performing an emotional empathy task, suggesting a lack of cortical top-down control of the frontal cortex on the limbic system (Pino et al. 2016).

Both the behavioral results and the altered functional patterns of activation in empathy-related brain structures may be associated with the reduced sleep quality in PTSD patients. In fact, sleep loss and sleep disturbances may alter the functional connectivity of the neural networks that are critical for emotional empathy, explaining the emotional and social difficulties experienced by individuals suffering from PTSD. Future neuroimaging studies in larger samples of PTSD subjects should shed light on this important issue.

Therefore, taken together, these evidence support the notion that sleep disturbances play a significant role in emotional processing in PTSD, suggesting the importance of preventive strategies to improve sleep quality in the aftermath of a stressful/traumatic event. Along this line of reasoning, treating sleep disturbances with a specific cognitive-behavioral therapy immediately after the trauma exposure may reduce the development of PTSD.

6.6 Conclusions

In the last two decades, a growing number of experimental investigations have focused on the relationship between sleep and emotional processing. In the present chapter, we have reviewed several studies supporting the notion that sleep is critical for several aspects of emotional regulation. It has been demonstrated that sleep affects the formation of emotional memories throughout all the stages of this process. In fact, as sleep loss deteriorates the encoding of emotional information, it leads to a disruptive interference with emotional memory consolidation.

The relationship between sleep and emotional memory processing is less clear in people with poor sleep quality. Indeed, we showed a preserved sleep-dependent consolidation of emotional information in poor sleepers, but a more negative

affective tone to memories. In this regard, converging evidence indicates that sleep loss significantly affects emotional reactivity. However, whether sleep acts to protect, potentiate, or de-potentiate emotional reactivity is still a matter of debate. Future studies will have to clarify, at the behavioral level, the specific direction of the sleep-dependent emotional modulation.

Moreover, sleep has been shown to have a key role both in complex emotional processes, such as those involved in empathy, and in more basic emotions such as fear. In this respect, sleep seems to be crucial for our ability to correctly process emotional information that allows us to understand the others' feelings and to be empathic with them, as well as for our ability to form and retain fear conditioning and extinction learning.

Notably, several studies have found REM sleep as the specific sleep stage responsible for an optimal emotional processing. In fact, the functional and neurochemical changes that characterize this sleep stage show a strong convergence with the brain mechanisms and substratum of emotional memory formation as well as appraisal during wakefulness. Although there is a general consensus on the role of REM sleep in the consolidation of emotional memory, to date the specific contribution of REM sleep on next-day emotional reactivity is less clear. In fact, REM sleep could act to potentiate or, conversely, de-potentiate the emotional charge associated to a memory along with its consolidation. This topic could be also relevant for its implications in clinical settings. Indeed, further expanding our knowledge on the relation between sleep and next-day emotional brain functioning will be crucial to open a new perspective for the understanding and treatment of affective or anxiety disturbances.

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Chapter 7
Sleep, Stress, and Traumatic Memory

L. D. Sanford, L. L. Wellman, G. Lonart, and R. J. Ross

Abstract Intense stress has the potential to produce traumatic memories that are core features of chronic mental disorders. However, encountering even intense stress most often does not have a persisting negative impact on health. Stress outcomes appear to involve complex interactions of sleep, learning, stressor qualities, and individual differences in resilience and vulnerability. This chapter will discuss how these interactions can impact the formation of traumatic memories, with a focus on factors that can differentially lead to normal and pathological stress outcomes. It will discuss the potential roles of different types of learning, stress resilience and vulnerability, and the neurobiological substrates that regulate interactions of stress, sleep, and the formation of traumatic memories. A case will be made that, given its role in learning and the processing of emotion, sleep may be key to fully understanding normal and pathological outcomes of intense stress.

Keywords Amygdala · Learning · Memory · Sleep · Stress · Synaptic plasticity

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L. D. Sanford (✉) · L. L. Wellman
Sleep Research Laboratory, Eastern Virginia Medical School, Norfolk, VA, USA

Department of Pathology and Anatomy, Eastern Virginia Medical School, Norfolk, VA, USA
e-mail: sanforld@evms.edu; wellmall@evms.edu

G. Lonart
Department of Pathology and Anatomy, Eastern Virginia Medical School, Norfolk, VA, USA
e-mail: lonartg@evms.edu

R. J. Ross
Research and Development Service, Corporal Michael J. Crescenz Veterans Affairs Medical Center, Philadelphia, PA, USA

Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA
e-mail: Richard.Ross2@va.gov

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7.1 Introduction

Real and perceived danger evoke a coordinated behavioral, neurobiological, and physiological stress response that provides resources for organisms to cope with an ongoing challenge and that enables physiological homeostasis to be restored when the threat is removed (Chrousos 1998; Chrousos et al. 2000). By definition, the stress response includes arousal (Chrousos 1998), and virtually all stressors are associated with significant alterations in sleep in the early post-stress period. Stressful events also provide the opportunity for learning and the formation of stress-related and fear memories that can impact the ability to respond to future challenges. Experimental evidence indicates that stress-related memories can themselves induce a stress response and can have much the same effects on behavior and sleep as the original stressor.

The stress response is normally adaptive and important for survival, and learning associated with successful coping can improve the ability to deal with subsequent stressors (Chrousos 1998). However, traumatic stress can overwhelm an individual's ability to cope, resulting in a stress response that is compromised or fails. In such instances, trauma-related memories have the potential to contribute to psychopathology and also are often a defining symptom.

Sleep is emerging as a significant biomarker of differential stress responses and as a putative mediator of stress outcomes. Indeed, sleep disturbances both before (Bryant et al. 2010; Gehrman et al. 2013) and after (Koren et al. 2002; Lavie 2001) a traumatic event may be predictive of emotional and physical disorders. Additionally, sleep has long been implicated in learning and memory consolidation, and recent studies have suggested that sleep, in particular rapid eye movement sleep (REM), is important for processing emotion (Goldstein and Walker 2014) and adapting to stress (Mellman et al. 2002, 2007; Sanford et al. 2010). REM can be increased or decreased in association with similar stress system activation and fear behavior (Sanford et al. 2010; Machida et al. 2013; Yang et al. 2011; Wellman et al. 2016, 2017), indicating complex relationships among sleep, stress, and learning that currently are poorly understood.

In this chapter, we will provide an overview of the relationships of stress, sleep, learning, and the formation of trauma-related memories, with the goal of delineating critical gaps in our knowledge of how traumatic stress can produce significant negative effects on emotional and physical health.

7.2 Stress Response

Stress is broadly defined as a nonspecific physiological response to a situation or event that is psychologically or physiologically demanding. In response to stressors, neurochemical mediators are released and act acutely to promote adaptive physiological and behavioral responses (McEwen 2007). These include activation of the

hypothalamo-pituitary-adrenal (HPA) axis and the autonomic nervous system (sympathoadrenalmedullary (SAM) branch) to initiate and regulate behavioral and physiological responses and adaptations to challenge (Chrousos 1998, 2009; Chrousos et al. 2000; Nezi et al. 2000). Other processes work to prevent over-responses of the stress systems (Chrousos 1998). Problems can arise when the stress response is insufficient or the stress system is overwhelmed by an intense or prolonged challenge (Chrousos 1998). Indeed, stress is implicated in a number of neuropsychiatric diseases as well as a variety of physical health ailments and risks. Traumatic stress leads to the development of posttraumatic stress disorder (PTSD) in a substantial minority of individuals and can be associated with depression as well.

7.3 Effects of Stress on Sleep

Essentially all stressors that have been examined produce alterations in sleep (for reviews, see Pawlyk et al. 2008; Sanford et al. 2015). Animal experiments have repeatedly demonstrated that stressful experiences during wakefulness can significantly impact subsequent sleep. Sleep has been recorded after a range of stressors, including avoidable footshock, restraint, water maze, exposure to novel objects, open field, ether exposure, cage change, and social stress (reviewed in Pawlyk et al. 2008; Sanford and Tang 2009). This work has described the effects of a variety of stressors on sleep and demonstrated that changes in arousal and sleep vary with stressor type and intensity. Effects also depend on the duration of stress exposure, with significant differences in the effects of acute compared to repeated or chronic stress (reviewed in Sanford et al. 2015). Repeated and chronic stress can produce alterations in sleep related to disruptions in homeostatic and circadian drive in addition to effects specific to stress (Sanford et al. 2015). For this reason, we will concentrate our discussion on the effects of discrete, temporally limited stressors, which enable clearer identification and definition of the stressful experiences.

Exposure to an acute stressor typically produces a period of arousal followed by subsequent increases in REM and/or non-REM (NREM) that occur at various latencies after the stressor is removed. In some cases, the amount of post-stress sleep can be larger than the amount lost; for example, the increase in NREM can be larger after an encounter with an aggressive conspecific than after an equal period of sleep deprivation (Meerlo et al. 1997; Meerlo and Turek 2001). The increase in sleep also can be significantly delayed even when the opportunity to sleep is available. While this delay can occur with a variety of stressors, it is perhaps best exemplified by restraint stress, in which case the application of restraint in the light period can produce an enhancement of REM in the following dark period (Meerlo et al. 2001; Rampin et al. 1991).

A pattern of initial arousal followed by recovery sleep is observed with minor and mild stressors (e.g., handling, novelty, open field) and stressors that animals may repeatedly experience (e.g., cage change); this suggests that this response pattern is not indicative of developing pathology. Relatively intense controllable stress

(modeled by escapable shock (ES)) can also be followed by a significant increase in sleep, particularly an increase in REM, which can occur soon after the stressor is removed. We (LDS and LLW) have suggested that the increases in sleep after many stressors may reflect restoration of homeostasis as the stress response follows its normal course (reviewed in Sanford and Tang 2009). The fact that sleep amount after stress can be greater than that lost is consistent with a significant role of sleep in the stress response. It has been suggested that REM plays a role in "decoupling" memory from its emotional charge (Baran et al. 2012; van der Helm et al. 2011; Walker and van der Helm 2009) and that intact REM may aid in the processing of the memory for trauma (Mellman et al. 2002, 2007). Based on work in animals, we (Sanford et al. 2010; Tang et al. 2005) and others (Suchecki et al. 2012) also have suggested that REM may have an adaptive function in recovery from stress. Some stressors (e.g., social stress (Meerlo et al. 1997; Meerlo and Turek 2001)) seem to preferentially promote NREM, suggesting that it as well may be important for recovering from certain types of stress. This would be consistent with the finding that both visually scored delta sleep and EEG delta amplitude may be reduced in individuals with PTSD (reviewed in Neylan et al. 2006).

7.4 Effects of Stress on Learning and Memory

Although stress can have a significant negative impact on health (Shalev 2000; Van den Berg et al. 1998; Van Dijken et al. 1992; Adamac and Shallow 1993; Pynoos et al. 1996), most stressors do not produce persisting or pathological changes. Even the extreme stress associated with traumatic life events gives rise to PTSD in only a minority of individuals (Yehuda and LeDoux 2007; Cohen et al. 2003; Kerns et al. 2004); most adequately cope with such experiences with only transitory detrimental effects. The difference between successful and unsuccessful coping with stress, including whether stress has transitory or lasting effects, can vary with characteristics of the stressful event including its controllability (Bolstad and Zinbarg 1997; Foa et al. 1992), predictability (Adell et al. 1988; Abbott et al. 1984), duration, and intensity (Buydens-Branchey et al. 1990; Natelson 2004). An individual's relative resilience and vulnerability are also of great importance (Yehuda et al. 2006). How these factors alter the potential pathological impact of stress is poorly understood, but it likely involves their impact on trauma-related learning and memory.

Stressful events can engage associative (operant (instrumental) and classical conditioning) and nonassociative (sensitization and habituation) learning processes; these different types of learning can occur concurrently, with tremendous importance for mediating stress outcome. Effective methods of avoiding long-term consequences of stress involve learning, with the formation of successful coping strategies. From an evolutionary perspective, this relationship between stress and memory is important as survival success depends on both the ability to respond to a current threat and the ability to use knowledge gained from prior experiences to meet future similar challenges (Salehi et al. 2010). An experimental example is found in studies

of stressor controllability, which have demonstrated that controllable and uncontrollable stress of the same magnitude can have significantly different impacts on behavioral and physiological outcomes (Bolstad and Zinbarg 1997; Foa et al. 1992). Uncontrollable stress has been linked to negative outcomes, including deficits in learning and in motivational and emotional functioning, and it can induce significant alterations in a variety of neurochemical systems. By comparison, controllable stress has been associated with neutral or positive outcomes. The ability, or inability, to learn and remember a successful coping response likely determines the different outcomes of controllable and uncontrollable stress.

Controllable stress, which can enable stress-related operant learning, can guide successful responses to future challenges. Conversely, uncontrollable stress has the potential to impede useful operant learning and can negatively impact the ability to respond to subsequent stress. Perhaps the best known paradigm for distinguishing the outcomes of exposure to controllable and uncontrollable stress is learned helplessness (Anisman and Merali 2009; Overmier and Seligman 1967; Seligman and Beagley 1975; Seligman and Maier 1967; Seligman et al. 1975). In one variant of this paradigm, experimentally yoked animals receive equal amounts of footshock, but one member of the yoked pair can terminate the footshock simply by moving to the safe side of the shock chamber (controllable stress), while the other member cannot act to influence the shock presentation (uncontrollable stress). Rodents that receive inescapable shock (IS) can show deficits in the ability to learn a subsequent escape response, whereas those that are able to escape from shock can show attenuated responses to subsequent uncontrollable shock presentations (reviewed in Anisman and Merali 2009). Interestingly, uncovering learning deficits in rodents that have experienced uncontrollable stress may require implementing a test with a more difficult escape contingency or one that requires a longer active response than that used in the original uncontrollable stress paradigm (Anisman and Merali 2009).

Stressful events may also engage classical conditioning processes. The most studied is fear conditioning, a widely used experimental model of learned fear and anxiety, with relevance to the development of mental disorders in humans, PTSD in particular (Foa et al. 1992; Davis 1990; Grillon et al. 1996; Shalev et al. 1992; Charney and Deutch 1996; Pitman et al. 2001). In experimental fear conditioning, an explicit neutral stimulus (generally a light or auditory stimulus) or situational context comes to induce fear through an association with an aversive stimulus (usually footshock) (Davis 1990; Davis and Whalen 2001). After the association is made, subsequent exposure to the newly fear-conditioned cue or context can elicit behavioral and physiologic responses similar to those elicited by the unconditioned aversive stimulus. These include behavioral freezing (absence of all movement except respiration) (e.g., Blanchard and Blanchard 1969; Paylor et al. 1994), a stress response (Yang et al. 2011; Wellman et al. 2016, 2017), a variety of physiological signals (e.g., increased heart rate and respiration) indicative of fear (reviewed in Davis 1992a), and a fear-potentiated increase in startle amplitude (Davis 1990, 1992b).

After training, fear-conditioned memories provide a pathway by which reminders of traumatic events can produce maladaptive changes in behavior. However,

conditioned fear also can underlie adaptive behavior that typically is extinguished when the fear-inducing stimulus is no longer presented (Pitman et al. 2001; Kishimoto et al. 2000). Indeed, it is the failure of fear extinction that has been linked to persisting symptoms of PTSD (Myers and Davis 2007), though the qualities of a stressful event that mediate adaptive and maladaptive fear responses are poorly understood. Contextual reminders of ES and IS, models of controllable and uncontrollable stress, respectively, can produce differential activation in brain stress regulatory regions (Liu et al. 2009a) and different sleep responses (Sanford et al. 2010; Yang et al. 2011, discussed below), whereas behavioral fear and stress indices can be virtually identical (Sanford et al. 2010; Machida et al. 2013; Yang et al. 2011). This suggests that successfully learning an escape response can differentially mediate several stress outcomes even though standard indices of fear and stress do not vary. Such learning, and the impact it would have on immediate stress outcomes and its potential for increasing the probability of successful responses to subsequent stressors, would provide a clear advantage to the animal.

Different from conditioning, sensitization is defined as enhanced responding upon repeated presentations of a stimulus, and habituation is defined as reduced responding with repeated stimulus presentations (Rahn et al. 2013). Exposure to extreme stressors has the potential to sensitize an organism's response to future stressors (Smid et al. 2012). Sensitization of various stress-related systems (e.g., HPA axis (Yehuda 2001), noradrenergic (NA) system (Southwick et al. 1994) and arousal/hyperarousal systems more generally (Rahn et al. 2013)), has been implicated in the development of PTSD (Shalev 2000). By comparison, habituation is important for reducing responses to repeated stressors of a similar type, thereby, for example, limiting the harmful effects of sustained glucocorticoid release (Herman 2013). Variants of exposure therapy are thought to rely partly on habituation (Sripada and Rauch 2015; Jaycox et al. 1998), as well as extinction learning (Hofmann 2007), to reduce fear responses.

It has been suggested that the pathophysiology of PTSD depends on complex interactions between associative and nonassociative learning arising from traumatic events (Siegmund and Wotjak 2006). Siegmund and Wotjak (2006) proposed a "Dual-Branch Hypothesis of PTSD" that incorporates fear conditioning and sensitization as mediators of associative and nonassociative fear memory, respectively. In this model, classical conditioning mediates associative fear memory and related processes including fear generalization, whereas sensitization mediates fear incubation. There is also evidence that sensitization can impact conditioned fear in some instances and that sensitization and habituation may play roles in mediating the magnitude of fear-induced freezing (Kamprath and Wotjak 2004).

In addition to the potential interactions or parallel roles of classical conditioned fear and sensitization in the formation of traumatic memories, our work with ES and IS demonstrates that differences in operant learning can differentially mediate several outcomes of acute stress even though standard measures of stress and fear may be the same across conditions (Sanford et al. 2010; Machida et al. 2013; Yang et al. 2011). For example, even in the IS condition, the animal typically attempts to escape or engage in other behaviors to try to lessen stressor intensity. Failed escape

attempts and inadequate behavioral responses may contribute to the formation and intensity of traumatic memories, whereas successful escape may ameliorate some effects of the stressful experience. In summary, the formation of traumatic memories potentially involves the collective effects of failed coping (operant) responses, intense fear conditioning, and stress-enhanced sensitization. These collective effects cross learning modalities and may make traumatic fear memories highly resistant to extinction. Unfortunately, the potential compound effects of, or interactions between, associative and nonassociative learning associated with stress have received little attention. Similarly, the role that sleep may play in processing traumatic memories and other posttraumatic behaviors has barely been explored.

7.5 Stress, Sleep, and Learning

There is considerable experimental support for a role for sleep in the consolidation of certain types of memories (see Born and Wilhelm 2012; Graves et al. 2003; Poe et al. 2010; Rolls et al. 2011; Stickgold 2005; Stickgold and Walker 2007; van Dongen et al. 2012; Walker 2009; for opposing opinions, see Siegel 2001, 2011; Vertes 2004a; Vertes and Siegel 2005). Most experiments have focused on the role that sleep may play in mediating performance on memory-related tasks in subsequent wakefulness. Less studied, and perhaps even less acknowledged, are the significant effects that emotional memories can have on sleep. However, answering complementary questions regarding the potential interactions between waking experiences and subsequent sleep is critical for fully understanding both the early effects of trauma and the development and persisting effects of traumatic memories.

7.5.1 Relationship Between Associative Learning and Memory and Sleep

Numerous studies using a variety of behavioral paradigms have demonstrated that learning experiences may be followed by alterations in subsequent sleep. One classical line of work employed shock avoidance training in a shuttle box, in which animals are signaled of imminent shock presentation and can learn to jump to safety preemptively. Successful avoidance is typically followed by a significant increase in REM at various times post-training, so-called REM "windows" (Smith and Butler 1982; Smith et al. 1974, 1980; Smith and Lapp 1986). These increases in REM have been viewed as evidence of a role for REM in memory consolidation. Consistent with this interpretation is the finding that selective post-training REM deprivation can adversely affect subsequent performance (Smith and Butler 1982; Smith and Lapp 1986; Smith and Kelly 1988). More recent work has suggested that pontine waves (the pontine component of ponto-geniculo-occipital (PGO) waves, a

neural signature of REM) may be the critical REM mechanism (Datta 2000; Mavanji and Datta 2003). Although shock avoidance generally has been viewed in the context of learning and memory, it is also a controllable stress paradigm that provides animals the opportunity to acquire a coping response to an aversive stimulus; an increase in REM follows successful acquisition of the avoidance response (Smith et al. 1980). Thus, shock avoidance is an excellent example of the impact of stress-related operant learning on sleep and of the potential role of sleep in mediating the formation and influence of stress-related memories.

Shock paradigms that model uncontrollable stress also can produce significant alterations in sleep. In an early study, Adrien et al. (1991) presented rats with 60 trials of IS at relatively high intensity (0.8 mA) and long duration (15 s) over the course of an hour. Compared to rats that experienced the shock chamber alone without receiving shock, rats trained with IS showed a greater REM latency and reduced REM amount during the 3 h after training. Subsequently, REM returned to the control amount, but no REM rebound was observed in recordings in the following dark or light periods. Light NREM amount was increased from baseline sleep and compared to the control group. This study demonstrates that strong uncontrollable stressful experiences can produce significant alterations in subsequent sleep. It also demonstrates a difference in sleep after avoidable shock, as well as many other stressors (discussed above), viz., lost REM was not recovered. Unfortunately, such studies typically do not examine the effects of stressful memories on sleep. Also, they usually focus on one type of learning, although as noted above, the response to intensely stressful experiences likely involves multiple types of associative and nonassociative learning.

One clear example of the effects of stress-related memory on sleep can be found in work using experimental fear conditioning paradigms. Fear conditioning models are important for examining the development and effects of traumatic memories as they can engage fear memory and induce fear and stress responses, and impact sleep, without requiring a full reexperiencing of the initiating stressful event. Indeed, various studies have used variations of cued and contextual fear conditioning to examine the effects of both fear conditioning and fear memories on sleep (e.g., Wellman et al. 2017; DaSilva et al. 2011; Laitman et al. 2014; Liu et al. 2002; Madan et al. 2008; Sanford et al. 2003a, b). However, general fear conditioning models, as currently conceived, are inadequate as they cannot fully explain the effects of stressful learning and memories on sleep, thereby indicating a significant gap in our understanding of how traumatic experiences can lead to persisting dysfunction in fear, stress, and arousal systems.

Although conditioned fear is thought to be important in the development of psychopathology, it is generally studied in animals using mild or limited shock presentations as the aversive stimulus. Such brief stressful experiences are not likely to produce the lasting changes necessary for the development of psychopathology in humans. Indeed, as indicated above, fear-conditioned responses typically extinguish when the fear-inducing situation is removed, and such extinction is thought to represent a form of successful adaptation to stress (Pitman et al. 2001; Kishimoto et al. 2000; Bouton 2004). On the other hand, DaSilva et al. (2011) have reported

that fear conditioning in the stress-sensitive Wistar–Kyoto (WKY) rat strain can produce the REM fragmentation similar to that reported in PTSD, particularly early in the course of the evolving PTSD symptom complex (Mellman et al. 2014; Ross 2014). Laitman et al. (2014) have provided preliminary validation of this model with their observation that prazosin, arguably the most effective treatment for the nightmare disturbance in PTSD, enhanced REM continuity in fear-conditioned WKY rats.

Mild conditioning produces relatively small effects on sleep. Using a single shock training paradigm, Hellman and Abel (2007) found that, in fear-conditioned mice compared to non-shocked mice as well as mice that experienced a footshock unassociated with conditioning, NREM was increased by approximately 1 h over the 24 h after training. However, the amount of training that an animal receives is an important parameter of the response to footshock stress. There appears to be a graded response in post-stress sleep that varies with number of stimulus-shock pairings. For example, the initial presentation of fearful cues after 4 days of IS training produced an 85% and a 55% reduction in REM and NREM, respectively, in the first hour after presentation (Sanford et al. 2003a), while the presentation of fearful cues after a single day of training produced a 34% and a 19% reduction in REM and NREM, respectively, in that time window (Sanford et al. 2003c). In contrast, REM and NREM in mice trained with a single cue-shock pairing did not significantly differ from baseline levels after the presentation of a single cue (Sanford et al. 2003c). Thus, multiple trial training appears to be required to produce alterations in sleep in response to fear-conditioned stimuli (Sanford et al. 2003c).

7.5.2 Stress Mediators and Sleep

Factors that can impact stress outcomes, such as stressor controllability and individual differences in resilience and vulnerability, can influence post-stress sleep. For example, controllable stress that is associated with positive or neutral outcomes can be followed by a significant increase in REM, whereas uncontrollable stress can decrease REM (Sanford et al. 2010; Machida et al. 2013).

The REM increase after controllable stress could be viewed as support for the oft-made argument that REM is needed for successful operant learning (Smith and Butler 1982; Smith et al. 1974, 1980; Smith and Lapp 1986; Smith and Kelly 1988), and REM may be involved in differences in learning. We (LDS and LLW) have recently found that outbred Wistar rats can show different REM responses to uncontrollable footshock stress. Some rats show pronounced decreases in REM during the first 4 h post-training, whereas others show no change or even an increase in REM (Wellman et al. 2016, 2017). These different REM responses (which we have called vulnerable and resilient REM responses) are independent of freezing and of stress-induced hyperthermia (SIH), a stress index that parallels the time course of the corticosterone response to stress (Groenink et al. 1994; Veening et al. 2004; Vinckers et al. 2009). Thus, REM may be a marker of differences in the stress

response that are not captured by standard behavioral and physiological measures of fear memory and stress (Wellman et al. 2016; 2017) or of operant learning.

7.6 Sleep as a Mediator of Memory and Stress Outcomes

The effects of experiences in waking on subsequent sleep have most often been examined in the context of the role sleep may play in forming associations and learning. Sleep deprivation after training can impair fear memory for a single shock training session (Graves et al. 2003; Hagewoud et al. 2010). A recent study in a rat model of circadian desynchrony found that fragmentation of NREM and REM without total sleep loss produced deficits in single-trial contextual fear conditioning, but not in cued fear conditioning or spatial learning (Lee et al. 2016). These and other studies (e.g., Cai et al. 2009; Fu et al. 2007) suggest that sleep may have a role in forming memories of transitory fearful events, which is consistent with the importance of sleep for adaptive learning.

There is evidence that REM promotes the consolidation of emotional memories (Genzel et al. 2015; Wagner et al. 2001). Menz et al. (2013) showed that, in healthy individuals, REM improved the recall of fear learned in a Pavlovian conditioning paradigm. Although these investigators emphasized the negative emotional consequences of REM-enhanced fear recall, Walker and van der Helm (2009) posited that REM following an aversive experience could reduce the negative emotional consequences of such fear recall. This is consistent with the suggestion of Bennion et al. (2015) that sleep-based facilitation of emotional memory processing involves a "restriction and refinement of the neural processes needed for *successful* [italices are the authors'] retrieval." Similarly, Rasch and Born (2013) suggested that, in traumatized individuals, a failure of the normal attenuation by REM of the negative tone associated with fear memories could produce a nightmare disturbance.

Using an experimental laboratory trauma protocol in healthy young women, Kleim et al. (2016) found that sleep posttrauma protected against the occurrence of intrusive trauma memories. Interestingly, it was NREM, including NREM fast parietal spindles, that was correlated with reduced intrusion frequency; REM density (no. rapid eye movements/total REM time) also was negatively correlated with frequency of intrusions. In a clinical study of accident survivors, REM fragmentation in the aftermath of trauma predicted the development of PTSD (Mellman et al. 2002), suggesting that uninterrupted REM is necessary for the effective processing of an emotional experience and the prevention of posttraumatic memories and other PTSD symptoms. The effects of REM on memory consolidation may extend beyond emotional memories. Studying healthy young adults, Whitehurst et al. (2016) found evidence that autonomic nervous system activity during REM, specifically vagally mediated activity measured as high frequency heart rate variability, played an important role in associative memory consolidation.

REM is marked by prominent electroencephalographic (EEG) activity in the theta band (4–12 Hz). Stujenske et al. (2014) have reviewed the evidence that theta band

oscillations in the basolateral amygdala (BLA), medial prefrontal cortex (mPFC), and hippocampus promote communication among these brain regions in response to aversive stimuli. In a polysomnographic study of healthy young adults who had been exposed to an environmental trauma, Cowdin et al. (2014) found that high right prefrontal theta power in REM was associated with resiliency. They concluded that theta power in this brain region could be a biomarker of a capacity for adaptive emotional memory processing. This interpretation is consistent with the earlier report by Nishida et al. (2009) that, in healthy young adults studied with a nap paradigm, high right prefrontal theta power in REM predicted improved consolidation of emotional, but not neutral, memories. There also is a report that memory for fear conditioning in rats trained in a relatively mild cued fear paradigm is associated with theta coherence in the amygdala, mPFC, and hippocampus during REM (Popa et al. 2010).

Stress and the stress hormone cortisol also are reported to influence memory consolidation (Bennion et al. 2015). There is evidence, although no consensus, that both enhance the consolidation of emotional memories (reviewed in Bennion et al. 2015). Cortisol level may be an important parameter (Lupien and Lepage 2001), with large elevations, that might occur during severe stress, impairing emotional learning. On the other hand, Zohar et al. (2011) found that administering a single dose of hydrocortisone to human subjects with symptoms of acute traumatic stress diminished the development of posttraumatic stress symptoms, i.e., possibly *enhanced* effective emotional learning. Similarly, van Marle et al. (2013) demonstrated a prioritization of emotional over neutral memory consolidation in healthy young males administered hydrocortisone; of particular interest, there was an attenuation of amygdalar activation during memory retrieval in these subjects, again suggesting that cortisol could enhance adaptive emotional learning.

An interaction between cortisol and sleep processes may be necessary for the consolidation of negative emotional memories (Bennion et al. 2015). Consistent with this hypothesis, Bennion et al. (2015) reported that cortisol was essential for sleep-facilitated memory consolidation in a population of healthy young adults. This dependence was especially strong when an aversive item was well attended at the time of encoding. Wagner and Born (2008) have suggested that the normal rise in cortisol late in the sleep period, when REM predominates, may "counteract an overshooting consolidation of emotional memories;" in hypocortisolemic conditions, such as PTSD has been construed, removing this cortisol "brake" may release intrusive distressing memories.

The above discussion illustrates the often conflicting results and hypotheses regarding the potential role of sleep and stress in mediating the formation of traumatic memories that may have other pathological consequences. Indeed, stress and fear learning systems may mediate *adaptive* responses that enable individuals to cope successfully with ongoing challenges as well as *maladaptive* responses that have the potential to contribute to pathology linked to traumatic memories. It is essential in both basic and clinical studies to distinguish adaptive from maladaptive stress responses and to determine the factors underlying each.

7.7 Neurobiological Distinctions Between Adaptive vs. Maladaptive Traumatic Memories

Memory formation depends on synaptic plasticity (Josselyn et al. 2015). The widely accepted synaptic plasticity and memory hypothesis states that "Activity-dependent synaptic plasticity is induced at appropriate synapses during memory formation, and is both necessary and sufficient for the information storage underlying the type of memory mediated by the brain area in which that plasticity is observed" (Martin et al. 2000). Formation of a memory trace, engram, involves changing synaptic weights within a neuronal circuit. Encoding of information during memory formation requires conversion of labile changes to more enduring changes in synaptic weight called synaptic/cellular consolidation. Consolidation of memory, in particular explicit associative memory, may also involve the distribution of the engram to different brain areas, often termed system consolidation. Memory also includes recall and reconsolidation of memory engrams. Thus, there are multiple opportunities for stress and sleep to have adaptive or maladaptive influences on memory processes.

7.7.1 Stress and Synaptic Plasticity

To limit our discussion, we will focus on how stress may influence the best characterized form of synaptic plasticity, NMDA receptor-dependent long-term potentiation (LTP) and long-term depression (LTD) of CA1 hippocampal neurons. In CA1, acute stress-evoked corticosteroids and catecholamines enhance LTP via mechanisms that include insertion of AMPA receptors into the postsynaptic site (O'Dell et al. 2015; Takeuchi et al. 2016; Groc et al. 2008). However, chronic stress, with elevated corticosteroid levels, may produce opposite effects, reducing AMPA and NMDA receptor levels (Alfarez et al. 2006); this leads to a decrease in dendritic spine size or density, a correlate of LTD. In contrast to the hippocampus, neurons in BLA, but not the central nucleus of the amygdala (CNA), undergo hypertrophy after chronic stress, exhibiting a region-specific response (Qin et al. 2011; Vyas et al. 2006). As discussed later, these are critical brain regions for linking fear memory and sleep.

In addition to the extensively studied corticosteroid- and catecholamine-mediated mechanisms and their signaling pathways, the integrated stress response that encompasses cellular responses to possibly all forms of stress is gaining increasing attention. It is an evolutionary conserved cellular mechanism for coping with stress, and it couples stressful components of a learning situation to synaptic plasticity. Interference with the integrated stress response pathway alters both synaptic plasticity and learning outcomes (Sekine et al. 2015; Jian et al. 2014). The molecular differences between adaptive and maladaptive responses to stress remain undetermined. However, it is intriguing that the integrated stress response involves

a global reduction in translation initiation, including synaptic plasticity genes, but preferential translation initiation of stress remediation transcripts (Young and Wek 2016). It is tempting to speculate that adaptive responses to stress involve faster stress remediation and less suppression of plasticity genes.

7.7.2 Sleep and Synaptic Plasticity

An increase in synaptic strength during learning and memory processes correlates with increased synapse numbers and synaptic size. However, physical constraints, such as the limited space within the adult cranium, and synaptic saturation, when efficacy of synaptic transmission is maximized, pose limits to increased synapse density and size as a lifelong learning mechanism. To counteract saturation of synaptic strength/size, there are synaptic homeostatic mechanisms. One of the possible benefits of sleep could be to restore synaptic homeostasis (Tononi and Cirelli 2014). During sleep, synaptic downscaling results in a net decrease in synaptic strength while maintaining relative differences between strongly vs. weakly potentiated synapses (de Vivo et al. 2017) in the neocortex, thus maintaining memory engrams.

Sleep may play a complementary plasticity inducing role in extrahippocampal cortical regions during hippocampus-dependent learning. Rat CA1 pyramidal neurons that are sequentially activated during spatial behavior repeat the same order of firing during subsequent NREM (Born and Wilhelm 2012). Such replay of this information in each NREM cycle, with information transfer from the hippocampus to extrahippocampal regions, induces plasticity in these regions, leading to extraction of semantic content of episodic memories. REM may also have a role in this process. Neuronal circuits reactivated in NREM are primed for LTP in the ensuing REM period, supporting plasticity-related gene expression (Ribeiro et al. 1999; Ulloor and Datta 2005). Thus, sleep interacts with plasticity processes that relate to memory formation in multiple ways. Sleep may contribute to the lifelong capacity for learning by facilitating homeostatic processes and system consolidation of memories. At the same time, learning experiences affect sleep parameters, probably using overlapping cellular mechanisms, potentially in ways that differentiate adaptive and maladaptive memories.

7.8 Neurocircuitry Linking Sleep, Stress, and Memory

Major components of the neurocircuitry linking stress, fear learning, and REM are known, and the roles of several brain regions have been established. These include the amygdala, hippocampus, and mPFC, which are important structures in fear memory circuitry and linked to brain stem regions involved in the response to stress and the regulation of REM.

The amygdala is critical for emotion. It is central in all models of fear conditioning (Davis 1992b; LeDoux 1992; LeDoux and Muller 1997) and important for the expression and extinction of fear (Buchel and Dolan 2000; LaBar et al. 1998; Linnman et al. 2011; Phelps et al. 2004; Sehlmeyer et al. 2009). It has been linked to mood and anxiety disorders as well as PTSD. Neuronal activity of the amygdala varies across the sleep-wake states, with increased activity during REM and less activity during NREM in comparison to wakefulness (Nofzinger et al. 2002; Braun et al. 1997), findings consistent with its significant role in modulating arousal and sleep in both normal and stressful conditions (Bernard et al. 1993; Krettek and Price 1978; Petrov et al. 1994; Peyron et al. 1998; Price et al. 1987; Sanford et al. 1995, 2002; Smith and Miskiman 1975). Our (LDS and LLW) recent work has demonstrated a role for the amygdala in regulating the impact of fearful memories on sleep, i.e., whether REM is increased or decreased following stress and the activation of stress-related fear memories (Wellman et al. 2016, 2017).

Hippocampal activity has been observed during fear behavior in imaging studies, and it has been linked to the contextual features associated with fear conditioning and expression (Sehlmeyer et al. 2009; Kalisch et al. 2006; Knight et al. 2009; Milad et al. 2007). It is also implicated in extinction training and recall (Milad et al. 2007, 2009), and there is evidence that sleep is important for consolidating hippocampal-dependent memory (Lee et al. 2016; Cai et al. 2009; Fu et al. 2007; Ruskin et al. 2004; Ruskin and Lahoste 2008). In humans, activity in the mPFC has been reported to be increased during extinction of fear behavior and recall of extinction (Phelps et al. 2004) and to be positively correlated with post-fear REM (Spoormaker et al. 2014). However, these paradigms used relatively brief training protocols that employed shock applied to the hand or wrist that was titrated based on the subject's perception to be "uncomfortable," rather than "painful." Thus, their relevance for the role of mPFC activity in mediating the relationship between sleep and traumatic memories is not fully clear.

The circuitry regulating stress and fear (Chrousos 2009; Sanford et al. 2015; Davis and Whalen 2001; LeDoux 1993, 2000; Pare et al. 2004) has significant overlap with, and impact on, brain stem regions that regulate arousal and sleep (e.g., REM regulatory and generator regions in the pons: locus coeruleus (LC), dorsal raphe nucleus (DRN), nucleus subcoeruleus (SubC), laterodorsal and pedunculopontine tegmental nuclei (LDT/PPT), and the reticularis pontis oralis (RPO) (Morrison et al. 2000; Xi et al. 2011; Zhang et al. 2012)). These same brain stem regions also have significant roles in mediating the stress response. Noradrenergic (NA) and serotonergic (5-HT) neurons in the stress-responsive LC and DRN, respectively, are virtually silent during REM, and their activation has long been thought to inhibit its generation (reviewed in Steriade and McCarley 1990). Essentially all current conceptions of REM generation and control involve models of the interactions and mutual inhibition among these pontine and mesopontine regions and neurochemical systems (e.g., McCarley 2004; McCarley and Hobson 1975; Datta 2010; Lu et al. 2006; Fuller et al. 2007; Dunmyre et al. 2014; Scammell et al. 2017). These models include inhibitory effects of REM-off neurons (LC and DRN), excitatory effects of REM-on neurons (LDT and PPT), and generation of REM

phenomena (RPO) (McCarley 2007). Some models of REM regulation also consider descending inputs to pontine/mesopontine areas from more rostral regions, primarily cell groups located in the hypothalamus (Dunmyre et al. 2014; Ramaligam et al. 2013). There is also more limited evidence of roles for the amygdala and mPFC (Ramaligam et al. 2013; Saper et al. 2010), which may have particular importance in mediating the effects of stress and fear memory on REM.

7.8.1 Amygdalar Modulation of Sleep, Fear, and Stress

The amygdala projects (via efferents from CNA or the lateral division of the bed nucleus of the stria terminalis (BNST), both considered extended amygdala) to areas that control sleep and arousal including the thalamus, hypothalamus, and brain stem regions. Functional studies in animal models have shown that the amygdala has a strong influence on REM and that it regulates the effects of stress, fear, and fear memory on REM.

The CNA appears to directly regulate REM and to mediate the effects of stress and fear memory on REM. For example, functional inactivation of the CNA with microinjections of the $GABA_A$ agonist muscimol produced a selective decrease in REM, whereas blocking GABAergic inhibition with the $GABA_A$ antagonist bicuculline increased REM (Sanford et al. 2002). That stress-induced inactivation of CNA is involved in stress-induced reduction in REM is also suggested by the absence of Fos expression (a marker of neural activation (Chowdhury et al. 2000; Cullinan et al. 1995; Watanabe et al. 1994; Zangenehpour and Chaudhuri 2002)) in CNA with conditioned fear (Liu et al. 2003) and by the finding that bicuculline microinjected into CNA attenuated the IS-induced reduction in REM (Liu et al. 2009b). Blocking CNA inhibition also reduced activation, as indicated by c-Fos activity, in the LC, consistent with the role of this nucleus in inhibiting REM. In contrast, microinjection of the $GABA_A$ agonist muscimol into the CNA did not alter the REM reduction typically observed following IS nor did it change c-Fos activity in the LC following fear conditioning (Liu et al. 2009b), suggesting that inactivation of CNA regulates the reduction in REM after IS.

The BLA appears critical for determining how fear memories affect sleep, likely via descending projections from the CNA and/or BNST. Inactivation of the BLA with microinjections of muscimol prior to IS blocked the post-training reduction in REM and attenuated freezing and the subsequent reduction in REM when animals were reexposed to the stressful environment (Wellman et al. 2014). However, microinjections of muscimol immediately following IS or prior to context reexposure blocked the reduction in REM without altering fear behavior or the stress response. BLA also appears to be a critical area for regulating the differences between vulnerable and resilient animals with respect to stress and fear-induced alterations in REM. This is indicated by the fact that inactivation of BLA prior to reexposure to the shock context attenuated the REM reduction in vulnerable rats, but did not significantly alter REM in resilient rats (Wellman et al. 2017).

Corticotropin-releasing hormone (CRH), a major mediator of the brain's response to stress, acts in the amygdala to regulate the alterations in sleep observed following stress. Microinjection of the CRH antagonist antalarmin into the CNA of rats prior to context reexposure blocked the fear-induced reduction in REM and attenuated c-Fos expression in regions important for REM generation and regulation (LC and DRN) and the stress response (paraventricular nucleus of the hypothalamus) (Liu et al. 2011). When microinjected into the BLA prior to IS, antalarmin blocked the IS-induced reduction in REM without blocking fear memory as indicated by contextual freezing (Wellman et al. 2013). In vivo microdialysis in BLA of rats showed an increase in the CRH level following fear conditioning, and this corresponded to freezing behavior during later cue presentations (Mountney et al. 2011). The effects of stress also involve descending CRH projections. Both the CNA (Van Bockstaele et al. 1998) and the BNST (Van Bockstaele et al. 1999) contain CRH efferents to the LC that increase the firing rate of LC neurons and subsequently the release of NA on upstream targets (including the PFC (Curtis et al. 1997) and hippocampus (Page and Abercrombie 1997; Palamarchouk et al. 2002)).

7.8.2 The Role of Medial Prefrontal Cortex in Modulating Sleep, Fear, and Stress

The mPFC has an established role in the perception of stressor control and the mediation of stressor consequences. For example, past exposure to a controllable stressor is generally protective during future stressful experiences, an effect believed to be mediated by the mPFC. Blocking activation of the ventral mPFC (mPFCv) with muscimol produced failure in escape learning in rats presented with ES, and greater fear conditioning in rats provided an opportunity to escape shock in a shuttle box. By comparison, mPFCv activation with the GABA antagonist picrotoxin prior to IS promoted escape learning, indicating that mPFCv activity could increase self-protective behavior even when the stressor is not controllable (Maier et al. 2006).

The protective effect of mPFC activation during controllable stress is thought to involve inhibition of the DRN (Amat et al. 2005). Electrical stimulation of projection neurons in mPFC led to inhibition of DRN 5-HT neurons, at least partially through GABA interneurons (Celada et al. 2001). IS compared to ES produced significantly greater activation of DRN 5-HT cells, as measured by c-Fos activity (Amat et al. 2005; Grahn et al. 1999). This increased activity subsequently induced a greater efflux of 5-HT into the mPFCv inhibiting local pyramidal neurons (Puig et al. 2005) and further contributing to differential activation of the mPFCv by stressors of differing controllability (Amat et al. 2005).

The mPFC has also been found to influence REM. A recent study found that lesions of the mPFCv in rats decreased REM, increased sleep fragmentation, and shortened REM latency (Chang et al. 2014). A possible role of the mPFCv in modulating fear-conditioned sleep is suggested by the report of a positive correlation

between mPFCv activity during conditioning and subsequent REM (Spoormaker et al. 2014). This influence on REM likely involves connections between the mPFCv and REM-off brain stem regions (Chang et al. 2014), although projections to BLA and CNA, or to GABAergic neurons in the intercalated nuclei that have inhibitory control over CNA output, could also play a role (Vertes 2004b).

Interestingly, projections from the LC and DRN to the mPFC promote wakefulness (Cid-Pellitero and Garzon 2011a, b), and CRH plays a role in mediating these effects. Injections of CRH into the LC increased NA release in the mPFC, an action blocked by co-administration of a CRH antagonist (Smagin et al. 1995). The release of 5-HT in the mPFC induced by stimulation of CNA was blocked by administration of a CRH2 antagonist into the DRN (Forster et al. 2008).

7.9 Neurocircuitry Underlying the Complex Relationship Between Fear Memory and Sleep

Despite clear linkages between the circuitries that regulate conditioned fear and REM, current models based on studies of immediate fear responses (i.e., freezing and autonomic responses) *do not* sufficiently explain the relationship between fear memory and sleep or the dissociation that can occur between fear behaviors in wakefulness and fear-induced alterations in sleep. There is a clear discrepancy regarding the role of CNA in regulating fear behavior in wakefulness and fear-induced alterations in REM, which can either be increased or decreased after fearful events. In current fear models, *activation* of CNA induces the generation of fear behavior and related physiological responses via descending brain stem projections (Duvarci et al. 2011). However, *inhibition* of CNA suppresses REM, and its activation (e.g., with electrical stimulation (Smith and Miskiman 1975)) can promote REM in some situations. Another discrepancy is found in the fact that inactivating BLA prior to recall of contextual fear can block fear-induced reductions in REM without altering fear behavior or the stress response (Wellman et al. 2017). Thus, significant work is needed to delineate the neural circuits and substrates that link stress, sleep, and fear memory.

7.10 Conclusions

Traumatic stress has the potential to produce chronic mental disorders, including PTSD, and to increase susceptibility to physical diseases. However, even intense stress is often encountered with no more than a transitory negative impact. Interactions between stressor parameters, sleep, and learning are likely important determinants of differential stress outcomes and whether or not PTSD develops. Stressful memories can increase or decrease REM in much the same way that the original

stressor does, suggesting that this sleep state has a unique relationship with the type of stressful memories that are formed. Whether it plays an active role in the adaptive processing of stressful experiences, or rather is an epiphenomenon, needs to be determined.

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Chapter 8
The Distinctive Role of NREM and REM Sleep in the Consolidation of Fear Memory

Munazah F. Qureshi, Deepika Kant, and Sushil K. Jha

Abstract Studies suggest that one-night sleep sufficiently evokes qualitative changes in the emotional memory systems and helps in remodeling the amygdalar and prefrontal neural circuitries after learning. REM sleep also potentiates the conditioned neural responses to fear mainly in the lateral amygdala, hippocampus, and medial geniculate nucleus. In addition, the coherence of oscillatory theta waves increases in the amygdala and hippocampus after conditioning, which presumably helps encode fear memory. Some of the symptoms of post-traumatic stress disorder (PTSD) such as hyperarousal reactions, flashing, and nightmare are developed as a result of over-consolidation of negative memories. Subjects falling into sleep soon after experiencing a life-threatening event may keep such negative emotional memories alive for years. Therefore, sleep deprivation following trauma can be one of the interventions to help prevent the development of PTSD. On the other hand, sleep architecture changes after the consolidation of fear memory. Within sleep, NREM sleep significantly increased, and REM sleep significantly decreased only after the consolidation of fear memory but did not change if the memory was impaired. Using the Bayesian law of conditional probability, we have observed that the consolidation of fear memory requires facilitated NREM sleep. In this chapter, we have reviewed the beneficial effects of sleep loss in the consolidation of fear-conditioned memory and sleep loss-mediated alteration in the possible underlying molecular mechanisms. We have also discussed that rats trained during the active phase exhibited better conditioning response compared to the rats trained during the inactive phase. In addition, we have discussed the correlation between augmented NREM sleep manifestations with the induced freezing response and Bayesian probabilistic theorem to predict, if within sleep, there is (a) a high probability of NREM sleep augmentation after the consolidation of fear memory and (b) a low probability of NREM sleep augmentation after impairment of fear memory.

Munazah F. Qureshi and Deepika Kant have equally contributed to this chapter.

M. F. Qureshi · D. Kant · S. K. Jha (✉)
Sleep Research Laboratory, School of Life Sciences, Jawaharlal Nehru University, New Delhi, India
e-mail: sushilkjha@mail.jnu.ac.in

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8.1 Introduction

Several studies suggest that post-learning sleep helps in better memory recall and task performance associated with different memory types such as declarative memory (Gais and Born 2004; Ellenbogen et al. 2006; Rasch et al. 2007; Lu and Goder 2012), procedural memory (Gais et al. 2000; Walker et al. 2003; Hill et al. 2008), trace-conditioned memory (Wamsley and Antrobus 2009), and emotional memory (Wagner et al. 2006; Holland and Lewis 2007; Walker and van der Helm 2009). Sleep deprivation alternatively impairs the consolidation of memory formation associated with these learning paradigms. For example, total sleep deprivation impairs consolidation of declarative memory (Backhaus et al. 2006), motor adaptation task memory (Hill et al. 2008), motor sequence task memory (Walker et al. 2003), visual discrimination task memory (Gais et al. 2000), and trace-conditioned memory (Chaudhury and Colwell 2002), while REM sleep deprivation induces memory deficit of spatial (Bjorness et al. 2005) and water maze learning (Smith and Rose 1996) tasks. In addition, it has been observed that reactivating the episodic memory's neural network during slow-wave sleep with cue helps reinforce memory retention (Rasch et al. 2007). These studies have thus demonstrated the significance of sleep in the consolidation of several discrete memory types.

Fear conditioning is a widely accepted model to study the neural basis of negative memory and has been used in numerous studies to explore the mechanisms that may underlie the psychophysiological changes associated with negative emotional memories (Madan et al. 2008). In fear conditioning, the neutral conditioned stimulus (CS) (e.g., tone, light, or context) is paired with an aversive unconditioned stimulus (US) (such as foot shock). Since both the stimuli are presented together during the conditioning, an emotionally neutral stimulus (context or tone/light) acquires aversive properties. The CS thus elicits fearful behavioral responses such as freezing, defecation, and piloerection. These responses are otherwise generated by the threatening stimuli (LeDoux 2000; Madan et al. 2008; Madan and Jha 2008). The information processing of emotion-event association is modulated by the hippocampus-dependent but amygdala-dominant memory system (Knight et al. 2009; Kuriyama et al. 2010). The basolateral amygdala and hippocampus seem to be the primary sites for cued and contextual fear conditioning, respectively, where the information of conditioned and unconditioned stimuli associations are formed and remain stored (Kim and Jung 2006).

Several factors including circadian phases influence learning and memory (Gerstner and Yin 2010). For example, rodents exhibit better learning of the active avoidance task if it is performed during their active phase and the passive avoidance task if it is performed during their rest period (Davies et al. 1973; Catala et al. 1985). Likewise, it has been reported that the circadian phase affects only the consolidation

of contextual fear memory but not the cued fear memory (Valentinuzzi et al. 2001). Furthermore, it has been reported that the hippocampal "per-2," a clock gene, is involved in the modulation of trace fear conditioning but not cued fear conditioning (CuFC) (Wang et al. 2009). Chaudhury and Colwell (2002) have reported that the circadian phases can also influence CuFC memory (Chaudhury and Colwell 2002). In subsequent studies, however, the similar effects of the time of day on fear conditioning were not observed at all (McDonald et al. 2002; Hagewoud et al. 2010).

Sleep is another factor, which potentially facilitates the consolidation of fearful memories and underlying neuronal plasticity (Hennevin et al. 1995, 1998; Graves et al. 2003; Vecsey et al. 2009). One study suggests that one-night sleep induces some discrete qualitative changes in the emotional memory system. It helps in remodeling the neural network in the amygdala and prefrontal cortex (Payne and Kensinger 2011). The conditioned neural responses to fear increase mainly in the lateral amygdala, hippocampus, and medial geniculate nucleus during REM sleep (Hennevin et al. 1995, 1998). The oscillatory theta rhythms, which possibly facilitate the consolidation of cued fear memories, exhibit increased coherence in the amygdalar and hippocampal circuitries after conditioning (Seidenbecher et al. 2003; Narayanan et al. 2007). Further, the consolidation of excessive negative memories includes many symptoms associated with post-traumatic stress disorder (PTSD) such as flashing, nightmare, hyperarousal reactions, etc. (Pitman 1989). Sleep soon after learning contributes in keeping the emotional memories alive for years (Wagner et al. 2006) suggesting that sleep immediately after experiencing a traumatic event may possibly contribute in developing PTSD in the traumatized patients. Therefore, sleep deprivation following trauma has been sought as an intervention to help prevent the development of PTSD (Wagner et al. 2006; Holland and Lewis 2007). On the other hand, sleep architecture changes after the consolidation of fear memory (Kumar and Jha 2012, 2017; Qureshi and Jha 2017). Within sleep, NREM sleep significantly increased, and REM sleep significantly decreased only after the consolidation of fear memory but did not change if the memory was impaired (Kumar and Jha 2017). Using the Bayesian law of conditional probability, we observed that the consolidation CuFC memory requires facilitated NREM sleep. In this chapter, we have reviewed the beneficial effects of sleep loss in the consolidation of fear-conditioned memory and sleep loss-mediated alteration in the possible underlying molecular mechanisms. We have also discussed that rats trained during the active phase exhibited better conditioning response compared to the animals trained during the inactive phase. In addition, we have discussed the correlation between augmented NREM sleep manifestations with the induced freezing response and Bayesian probabilistic theorem to predict, if within sleep, there is (a) a high probability of NREM sleep augmentation after the consolidation of fear memory and (b) a low probability of NREM sleep augmentation after impairment of fear memory.

8.2 Sleep Deprivation and Alteration of Fear Memory

Sleep deprivation is a standard method to study the role of sleep in learning and memory processes. Various studies have shown that sleep deprivation shortly after acquiring a new task has an adverse effect on memory consolidation.

8.2.1 Short-Term Sleep Deprivation Soon After Training Impairs the Consolidation of Fear Memory

Total sleep deprivation soon after fear conditioning induces memory deficit in rodents. Freezing is a hallmark of fear conditioning. We have reported that sleep-deprived animals showed a marked decrease in freezing response as compared to non-sleep-deprived and stress control animals (Kumar and Jha 2012; Qureshi and Jha 2017). Earlier it was reported that sleep deprivation selectively impairs contextual fear memory but not cued fear memory (Graves et al. 2003; Ruskin et al. 2004). Our report, however, suggests that sleep deprivation also alters cued fear-conditioned memory (Kumar and Jha 2012). We have observed that sleep-deprived, non-sleep-deprived, and stress control animals exhibited almost similar freezing response during the initial 5 min of CS presentation, but sleep-deprived animals showed a dramatic reduction in freezing response 5 min after the tone inception (Kumar and Jha 2012). In earlier studies, the freezing response to CS was assessed only during 2–3 min after tone presentation (Graves et al. 2003; Ruskin et al. 2004). However, we observed that a significant decrease in freezing response in cued-fear-conditioned and sleep-deprived animals occurred outside the 2–3 min time window.

Short-term total sleep deprivation also alters contextual fear memory (Fig. 8.1). Sleep deprivation for 5 h soon after contextual fear conditioning impairs contextual fear memory (Graves et al. 2003; Qureshi and Jha 2017). However, Cai et al. 2009 have reported that sleep deprivation does not induce a deficit in contextual fear memory (Cai et al. 2009). Cai et al. have used highly anxious mice strain *C57BL/6Jx129T2SvEms* in their study, whereas, Graves et al. and we have used low and moderately anxious mice. The highly anxious mice demonstrate fearful behavior even with gentle handling, and it is, therefore, challenging to assess the effects of sleep deprivation on the consolidation of fear memory in them.

8.2.2 Sleep Deprivation Performed 5 Hours After Training Does Not Impair Fear Memory

It will be intriguing to see if there is a specific time window soon after training, during which, the memory is susceptible to sleep deprivation. It has been found that animals sleep deprived 5–10 h after training did not alter fearful memory. The

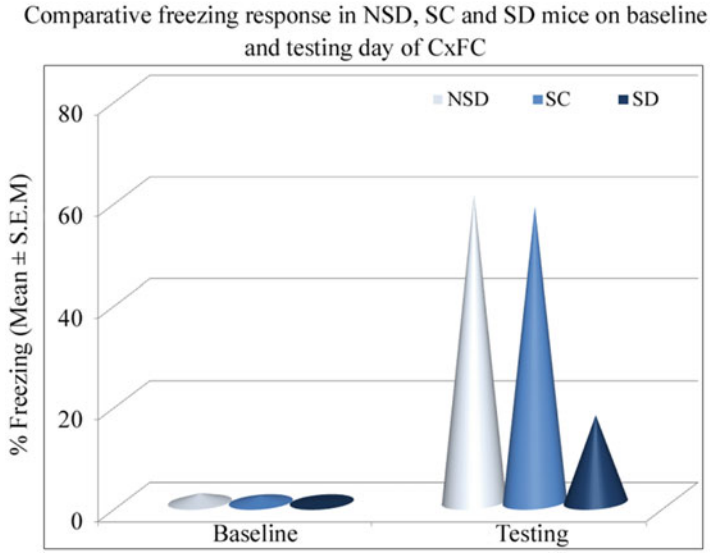

Fig. 8.1 The percent freezing response in the NSD, SC, and SD animals before and after contextual fear conditioning. The NSD, SC, and SD animals exhibited a comparable freezing response on the baseline day. The NSD and SC animals showed an increased freezing response on the testing day. Interestingly, the SD animals exhibited significantly less freezing response ($p < 0.001$, $F_{(2,18)} = 13.82$) as compared to the NSD (Tukey $p < 0.001$) and SC (Tukey $p < 0.01$) animals on the testing day. Abbreviations: *NSD* non-sleep-deprived animals, *SC* stress control animals, *SD* sleep-deprived animals. (Adapted from M. Quereshi's PhD Thesis)

induced freezing response in an altered context in sleep-deprived mice was also comparable to that of non-sleep-deprived animals. Furthermore, the freezing response to the cue was also comparable in the sleep-deprived and non-sleep-deprived mice. These findings suggest that sleep deprivation 5 h after training does not impair fearful memory (Graves et al. 2003).

8.2.3 Effect of Sleep Deprivation and Altered Circadian Cycle on Fear Memory

Sleep plays an essential role in the consolidation of fear memory but, during which circadian phase, is still debatable. Six-hour sleep deprivation immediately after training during the daytime impairs the consolidation of contextual fear memory. However, 6-h sleep deprivation soon after conditioning performed just before the dark onset did not induce memory deficit. Hagewoud et al. (2010) have observed that 6-h sleep deprivation during the night did not induce learning deficit, but 12 h of sleep deprivation indeed caused impairment (Hagewoud et al. 2010). Several other studies also support the view that 6-h sleep deprivation after training during the dark

phase did not induce memory deficit. Six-hour sleep deprivation soon after training in a novel object recognition task at the dark onset period does not affect recognition memory in rodents (Halassa et al. 2009; Palchykova et al. 2009). However, prolonged sleep deprivation after training during the night does impair memory consolidation. Rats sleep less (20–35%) during the dark phase compared to the light phase (65–80% (Borbély and Neuhaus 1979; Lancel and Kerkhof 1989). Therefore, it was argued that the amount of sleep loss during the 6-h sleep deprivation in the dark period is significantly less than the same period of sleep deprivation during the light period. The detrimental effect of sleep deprivation on memory consolidation hence depends on the total amounts of sleep loss during the deprivation period. Also, 6-h sleep deprivation during the late dark phase did not cause memory deficit, but 12-h sleep deprivation immediately after the training during the entire dark period impairs memory. Therefore, it has been proposed that the amount of sleep loss during deprivation is crucial for inducing the detrimental effect of sleep deprivation irrespective of the time of day.

It is not clearly known why sleep is required for memory consolidation. One of the possible explanations could be that sleep may be facilitating memory consolidation by preventing memory interference, which otherwise frequently occurs during wakefulness (Ellenbogen et al. 2006). The ongoing memory can be disrupted during wakefulness mainly due to the processing of various other sensory inputs associated with new experiences. It is also argued that sleep deprivation possibly blocks memory consolidation because of the stress allied with forced wakefulness. If it may be the reason, then sleep deprivation performed, either during the day or night, should have a similar detrimental effect on memory consolidation. But, studies have shown that 6-h sleep deprivation performed by gentle sensory stimulation during the day impairs memory consolidation but not during the dark period, even when the amount of stimulation used under both the conditions matches precisely. Six hours of sleep deprivation during the day and 12 h of sleep deprivation during the night may cause a comparable amount of sleep loss. Therefore, the disruption in memory formation can be attributed to the amount of sleep loss during the deprivation rather than the stress associated with forced wakefulness.

Alteration in the circadian cycle can also influence learning. We have reported that animals conditioned to fear during the night exhibit significantly better conditioning than the animals conditioned to fear during the daytime (Kumar and Jha 2012). Further, we have examined the combined effects of sleep loss and altered circadian phase on fearful learning. Animals were randomly divided into four groups: (a) non-sleep-deprived (NSD) group, (b) extended light period (ELP) group [animals were kept under constant 18 h light (12 h during the daytime +6 h during the dark period)], (c) stress control (SC) group (animals were kept in a movement restricted chamber for 6 h soon after contextual fear conditioning), and (d) sleep-deprived-extended light period (SD-ELP) group (animals were sleep deprived for 6 h soon after contextual fear conditioning under 6-h extended light condition). The percent mean (± SEM) conditioned freezing response in NSD, ELP,

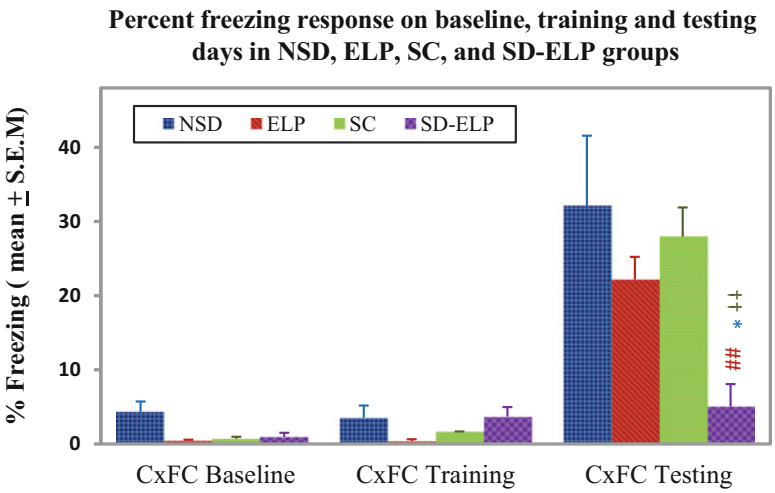

Fig. 8.2 Changes in % freezing response in NSD, ELP, SC, and SD-ELP animals on baseline, training, and testing day. SD-ELP animals exhibited significantly less freezing on CxFC testing day compared to NSD, ELP, and SC animals [$p < 0.05$, $F_{(1,15)} = 7.29$ compared to NSD animal; $p < 0.01$, $F_{(1,13)} = 22.12$ compared to SC animal; $p < 0.01$, $F_{(1,13)} = 15.12$ compared to ELP animal] (*one-way ANOVA followed by Tukey* post hoc *test*). Percent freezing response among NSD, ELP, and SC animals was statistically not significant on post-conditioning day. Percent freezing response on baseline and training days were comparable in all groups. * means $p < 0.05$ compared to NSD group. ## means $p < 0.01$ compared to ELP group. †† means $p < 0.01$ compared to SC group. Abbreviation: *CxFC* contextual fear conditioning, *NSD* non-sleep- deprived, *ELP* extended light period (7:00 PM–1:00 AM), *SC* stress control, *SD-ELP* sleep deprivation during extended light period (7:00 PM–1:00 AM). (Taken from G. Singh's PhD Thesis)

and SC groups were 32.00 ± 9.46, 22.15 ± 3.08, and 27.00 ± 3.93, respectively. However, SD-ELP animals demonstrated significantly less freezing ($5.05 \pm 3.02\%$) compared to NSD ($p < 0.05$; $F_{(1,15)} = 7.29$), ELP ($p < 0.01$; $F_{(1,13)} = 15.12$), and SC ($p < 0.01$; $F_{(1,13)} = 22.12$) (one-way ANOVA followed by Tukey post hoc test) groups during the post-conditioning day (Fig. 8.2). The SD-ELP animals exhibited 89.83%, 72.20%, and 81.30% less freezing compared to NSD, ELP, and SC animals. Freezing response within groups was not significant on the baseline and training days. Animals in the ELP group also exhibited significantly more freezing ($p < 0.001$; $F_{(1,11)} = 49.69$) (one-way ANOVA followed by Tukey post hoc test) on post-conditioning day compared to their baseline day. This suggests that extended light period (6 h) during active phase does not induce learning deficit. Similarly, SC group of animals also exhibited significantly more freezing response ($p < 0.001$; $F_{(1,11)} = 47.74$) (one-way ANOVA followed by Tukey post hoc test) on post-conditioning day suggesting that mild stress does not induce learning deficit. These results suggest that short-term sleep deprivation (6 h) with altered circadian phase induces learning deficit of fearful memory.

8.3 Molecular Mechanisms of Sleep-Dependent Memory Consolidation

The consolidation of fearful memory occurs over a period of hours to days and possibly depends on the short- and/or long-term reversible changes in the neuronal properties. Neuronal plasticity with increased synaptic strength is one of the underlying mechanisms of memory consolidation (Kushner et al. 2005). It has been observed that glutamatergic receptors are selectively upregulated in the synapses, which are involved in the processes of synapse strengthening after learning (Ljaschenko et al. 2013). Further, the sequence of neuronal activation seen during learning reoccurs during the post-learning sleep period as well. Several studies have provided evidence that the cellular and molecular events, which take place during learning, are replayed during post-learning sleep. We discuss below some of the molecular events, which are possibly associated with sleep-dependent memory consolidation.

8.3.1 Sleep Deprivation Alters N-Methyl-D-Aspartate (NMDA) Receptor and α-Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic Acid (AMPA) Receptor-Mediated Plasticity

All the three stages of memory, acquisition, consolidation, and retrieval require NMDA receptor activity. The consolidation phase, in which the memory transforms from labile to a stable state, requires significant NMDAR activity (Hernandez and Abel 2011). NMDARs increase Ca^{2+}influx into the cells and thus help induce the phenomenon of long-term potentiation (LTP) (Xia and Storm 2012). Sleep deprivation seems to affect the NMDAR activation by altering receptor subunit composition, surface expression, and hence, reduced Ca^{2+} influx (Chang et al. 2012). It was found that 72 h of sleep deprivation not only reduced the NMDA/AMPA receptor ratio in the hippocampal CA1 pyramidal cells in response to Schaffer collateral stimulation but also reduced the amplitude of NMDA receptor-mediated currents in the distal dendrites of CA1 neurons in the hippocampus. The reduction in the amplitude of NMDA receptor-mediated currents is primarily due to a reduction in the surface expression of NMDA receptors after sleep deprivation. It was observed that the majority of NR1 and NR2A subunits of NMDA receptors were present in the cytoplasm after sleep deprivation suggesting that the surface expression of NMDARs is altered in sleep-deprived animals (McDermott et al. 2006). Prolonged sleep deprivation (24 h) also disrupts NMDAR trafficking to the cell surface and a reduction in NMDA receptor-mediated current (Chen et al. 2006). Few other studies have also observed a sleep deprivation-induced reduction in NR1 subunit expression in the hippocampus. Apart from effects on NMDARs, sleep deprivation also causes

reduced phosphorylation of the GluR1 subunit of AMPA receptors (AMPARs) in the hippocampus. The phosphorylation at S845 is a prerequisite for the incorporation of AMPAR in the synaptic membrane. In addition, dephosphorylation of S845 may increase endocytosis of GluR1 containing AMPA receptors from the membrane. A reduction in phosphorylation of S845GluR1 after sleep deprivation suggests that sleep deprivation possibly alters the incorporation of GluR1 containing AMPA receptors in the membrane (Havekes et al. 2007).

8.3.2 Sleep Deprivation Alters and Attenuates mTOR Expression and Its Signaling

Mammalian target of rapamycin (mTOR) is a key regulator of the translational machinery. Translational regulation in the hippocampus is one of the key steps in memory consolidation (Bekinschtein et al. 2007). Sleep deprivation alters the levels of several proteins such as mTOR and 5′-adenosine monophosphate-activated protein kinase (AMPK). Short-term sleep deprivation decreases not only the total mTOR levels, but it also causes a huge decrease in phosphorylated mTOR level. The changed levels of total as well as phosphorylated mTOR return to their basal level after recovery of sleep from deprivation. These findings suggest that the decreases in total and phosphorylated mTOR could be exclusively associated with sleep loss (Vecsey et al. 2012). The two functionally distinct complexes of mTOR are mTORC1 and mTORC2, in which mTOR remains associated with Raptor and Rictor, respectively. Interestingly, it has been found that 5 h of sleep deprivation specifically decreased mTORC1 level, whereas mTORC2 remains unaltered. The kinase complex mTORC1 phosphorylates and inhibits the translation initiation factor 4E-binding protein-2 (4EBP2) and thereby initiates protein synthesis. The phosphorylated 4EBP2 does not bind to eukaryotic translation initiation factor 4E (eIF4E) and thus allows its binding to eukaryotic translation initiation factor 4G (eIF4G) and trigger translation. AMPK inhibits mTORC1 activity directly as well as indirectly. AMPK inhibits mTORC1 activity indirectly by activating the tuberous sclerosis complex (TSC) or directly by phosphorylating Raptor. It has been shown that 5 h of sleep deprivation significantly increased AMPK phosphorylation and significantly decreased the amount of phosphorylated 4EBP2 in the hippocampus. It has been found in sleep-deprived animals that mTORC1 activity, as well as the level of 4EBP2 phosphorylation, decreases in the hippocampus, suggesting that sleep deprivation could alter the binding efficacy of eIF4E with eIF4G. In a subsequent study, it was clearly shown that 5 h of sleep deprivation reduces eIF4E-eIF4G association in the hippocampus in mice. Therefore, it seems that sleep deprivation alters protein synthesis by influencing the AMPK-mTORC1-4EBP2 signaling pathway. Overall, these findings suggest that sleep deprivation targets 4EBP2-regulated protein synthesis resulting in sleep deprivation-induced memory deficit (Tudor et al. 2016).

8.3.3 Sleep Deprivation Alters Translational and Transcriptional Machinery

Sleep deprivation alters the expression of several genes. The most prominent downregulated gene clusters after sleep deprivation are (1) *Usp2*, *Usp24*, *Usp3*, and *Usp34* genes, which are involved in the regulation of ubiquitination/proteolysis; (2) *Eif2a*, *Eif3s6ip*, *Eif4el3*, and Eif5 genes associated with translation initiation factors; (3) mRNA processing and transport associated genes (*Rbm3* and *Denr*); (4) the nuclear mRNA shuttle *Hnrpdl gene*; and (5) *Cirbp* and *Rbm3* gene associated with cold-induced RNA-binding proteins. In addition, some other gene clusters such as AMP-activated kinase (AMPK) *Prkaa2* gene; *Vldlr* a very low-density lipoprotein receptor gene; genes associated with histone deacetylase activity such as *Sirt5*, *Sirt7*, *Hdac3*, and *Hdac9*; and ion-binding protein classes that require ion cofactors such as *Prkaa2*, *Kcnv1*, *Kcnk2*, *Camk4*, *Zswim1*, and *Nfx1* are also downregulated after sleep deprivation. Few of the gene clusters are upregulated after sleep deprivation, which are (1) nucleosomes/chromatin assembly having *Elk1* and *Fos* as transcription factors; (2) *H2afj*, *Hist1h2bc*, and *Hist3h2a* genes of histone family members; (3) *Rab8b*, *Rab15*, and *Rab21* genes of RAS oncogene family; and (4) *Hspa8*, *Hsp110*, and three *Hsp40* homologs from heat shock family of proteins. Some other genes such as (1) *Fos*, *Elk1*, *Nr4a1*, *Creb1*, and *Crem* associated with transcription factors and positive regulation of transcription; (2) *Nr4a1*, *Lats2*, and *Dusp19* genes involved in the negative regulation of kinase activity; and (3) genes associated with ion-binding (*Adamts2* and *Lats2*) and ATP/nucleotide binding (*Hspa8*, *Lats2*) are also upregulated after sleep deprivation (Vecsey et al. 2012). These studies have demonstrated that sleep deprivation simultaneously downregulates the gene clusters associated with the translation initiation genes and RNA-binding genes (many of which help mRNA to shuttle from the nucleus to ribosomes for translation) and upregulates the genes associated with the unfolded protein response. This suggests that inadequate sleep and sleep disturbances can directly alter the expression of many genes and proteins.

8.3.4 Sleep Deprivation Impairs cAMP Signaling

Sleep deprivation significantly reduces many signaling molecules including PKA activity and cAMP levels in the hippocampus. The levels of calcium and adenylyl cyclase enzyme, which are involved in the production of cyclic adenosine monophosphate (cAMP), transiently increase after learning (Xia and Storm 2012). The cAMP activates mainly three downstream targets, which play an essential role in protein synthesis as well as in memory consolidation: (a) protein kinase A (PKA), (b) exchange protein activated by cAMP (Epac), and (c) hyperpolarization-activated

cyclic nucleotide-gated channels (HCN) (Arnsten 2007). These downstream targets, along with other kinases, for example, calmodulin-dependent protein kinase (CAMKII), extracellular signal-regulated kinase (ERK1/ERK2), and mitogen-activated protein kinase (MAPK), are activated, which are primarily involved in the phosphorylation of transcription factors and in turn involved in protein translation (Enslen et al. 1994). It has been reported that the transcription factor "cAMP response element binding protein" (CREB) plays an essential role in memory conversion from a labile form to a stable state. Sleep deprivation significantly reduces both cAMP levels and PKA activity in the hippocampus, thereby, disrupting the downstream signaling pathway. Also, sleep deprivation alters phosphorylation of CREB by PKA at serine 133 in the hippocampus (Vecsey et al. 2009).

Phosphodiesterase-4 (PDE4) enzyme periodically degrades cAMP and thus plays an essential role in maintaining an optimum balance between PKA activity and cAMP. The level of cAMP decreases after sleep deprivation because of the increased activity of PDE4. Protein expression of PDE4A5, an isoform of PDE4, increases after short-term total sleep deprivation (Vecsey et al. 2009). It has also been found that blocking the PDE4 signaling during sleep deprivation rescues sleep deprivation-mediated deficit in LTP induction as well as the hippocampus-dependent memory consolidation suggesting that sleep deprivation alters cAMP-PKA pathway, which in turn affects memory.

8.3.5 Sleep Deprivation Increases Inhibitory G Protein-Coupled Receptor (GPCR) Signaling

Adenosine through its "A1" receptor activates Gi proteins and inhibits cAMP production in the cells. The extracellular levels of adenosine increase in the brain with increased metabolism (Radulovacki 1985). It has been found that the adenosine levels increase during wakefulness and decrease during sleep, and an increased level during wakefulness augments sleep drive (Porkka-Heiskanen et al. 1997). It has been reasoned that the prolonged wakefulness increases adenosine level, which acts through its A1 receptors and causes neuronal hyperpolarization and attenuation in neurotransmitter release around the surrounding excitatory presynaptic terminals (Newman 2003). The adenosine receptor A1 is coupled with Gi proteins resulting in the inhibition of cAMP production. Therefore, it is possible that the increased adenosine level with prolonged wakefulness will lead to increased G protein-coupled receptor (GPCR) signaling and decreased cAMP levels. The decreased cAMP levels would eventually impair memory consolidation. Caffeine, a nonselective A(1)/A(2) adenosine receptor antagonist, improves cognitive performance in humans. It facilitates memory retention when administered immediately after training, but not when administered 3 h later (Kopf et al. 1999).

8.3.6 *Restoration of Sleep Deprivation-Mediated Impairment in Memory Consolidation*

Sleep deprivation-mediated detrimental effects on memory consolidation can be rescued by activating specific molecular pathways associated with learning (Fig. 8.3). CREB-mediated gene transcription is one of the underlying mechanisms of long-term memory formation (Vecsey et al. 2007). An increased cAMP level activates PKA, which in turn enhances CREB-mediated gene transcription. Therefore, one possible mechanism for restoring the sleep loss-mediated impairment in memory consolidation could be the increased levels of cAMP in the hippocampus during sleep deprivation.

It has been reported that sleep deprivation associated deficits in cAMP signaling, synaptic plasticity, and hippocampus-dependent memory can be recovered if the animal is treated with PDE inhibitor (Vecsey et al. 2009). The memory

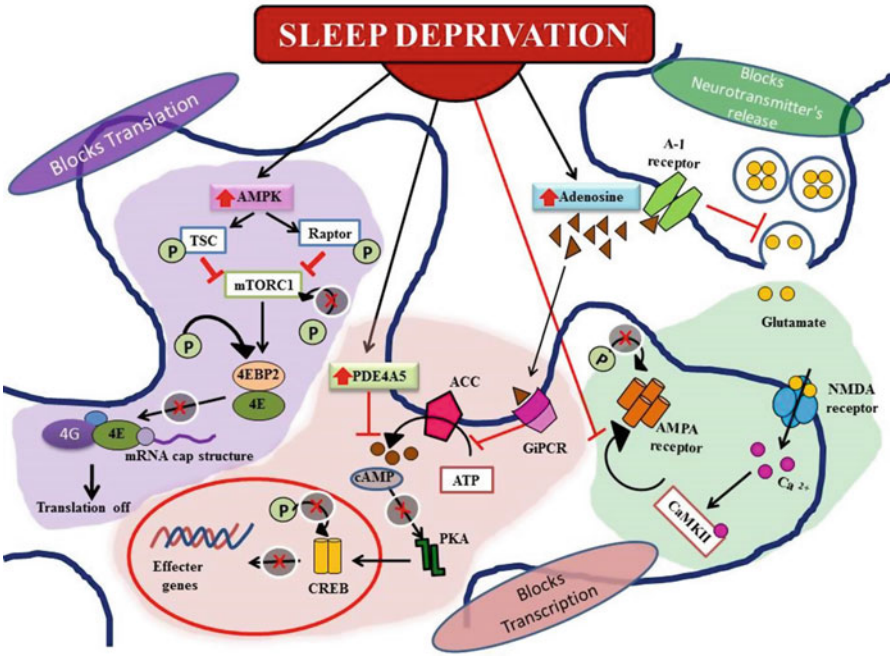

Fig. 8.3 A model showing that sleep deprivation affects transcriptional and translational machinery as well as neurotransmitter release in the neurons. (i) Sleep deprivation attenuates protein synthesis initiation by altering the AMPK-mTORC1-4EBP2 signaling pathway and eIF4E-eIF4G association in the hippocampus. (ii) In addition, sleep deprivation significantly reduces both, cAMP level and PKA activity in the hippocampus, thereby disrupting the downstream signaling pathway. Sleep deprivation also alters phosphorylation of CREB by PKA in the hippocampus. (iii) Sleep deprivation causes reduced phosphorylation of the GluR1 subunit of AMPA receptors in the hippocampus and thus impairs the recruitment of AMPA receptor in the membrane

consolidation processes become resistant to sleep loss after systemic injections of the nonspecific PDE4 inhibitor rolipram (Vecsey et al. 2009). It suggests that sleep deprivation alters the cAMP signaling, which may cause memory deficits. The increased adenosine level during prolonged forced wakefulness inhibits cAMP production through the activated adenosine A1 receptors. A1 receptors inhibit the production of adenylyl cyclase and thus decrease cAMP levels in the neurons. Interestingly, the chronic infusion of "8-cyclopentyl-1,3-dimethylxanthine" (CPT), a blocker of adenosine A1 receptor, prevents the sleep deprivation-mediated alteration in the memory consolidation and induction of hippocampal LTP (Havekes et al. 2012). It has also been reported that caffeine (an A1 receptor antagonist) helps prevent the sleep loss-mediated detrimental effects on the hippocampal synaptic plasticity and memory (Alhaider et al. 2011). Caffeine inhibits phosphodiesterase (PDEs) (such as PDE1, PDE4, and PDE5) and also promotes calcium release from intracellular stores and thereby helps in memory consolidation (Wu et al. 2009; Ribeiro and Sebastiao 2010).

The GluA1 subunit of the AMPA receptor is another candidate in the cAMP-PKA signaling pathway, which is involved in memory consolidation and synaptic plasticity (Havekes et al. 2007). Sleep loss impairs memory consolidation by reducing hippocampal AMPAR functioning including AMPAR GluA1 phosphorylation (Hagewoud et al. 2010). Therefore, if the levels of cAMP levels are increased with pharmacological intervention during sleep deprivation, it may restore the functioning of AMPAR and, in turn, facilitate memory consolidation. It, however, needs to be determined, if the increased cAMP levels during sleep deprivation reestablish the functions of AMPAR and levels of CREB and phosphorylated PKA and Epac substrates and rescue the sleep deprivation-induced memory deficit.

Histone deacetylase (HDAC) inhibitors can also be one of the potential candidates, which can restore sleep deprivation-mediated memory deficit. The administration of HDAC inhibitors reinstates learning-induced gene expression and memory function in aged animals (Peleg et al. 2010). Suberoylanilide hydroxamic acid (SAHA) is the first of the new HDAC inhibitors, which is being used to restore pathophysiology in cancer patients (Dokmanovic et al. 2007). It is also now well known that epigenetic machinery regulates contextual fear memory, and histone acetylation, specifically of H4K12, significantly increases after contextual fear conditioning (Peleg et al. 2010). Our lab has also further investigated (a) the effects of short-term sleep deprivation in an extended light period on acetylation of histone H4K12 soon after fear conditioning and (b) the role of HDAC inhibitor SAHA in rescuing the alteration in fear memory after sleep deprivation under altered circadian conditions (SD-ELP). We found that SAHA microinjection in the hippocampus soon after fear-conditioned training in the SD-ELP animals rescued sleep deprivation-dependent learning impairment. The SAHA-treated SD-ELP animals exhibited significantly more freezing response as compared to the vehicle-treated SD-ELP animals (Fig. 8.4).

Further, we observed that the acetylation of H4K12 significantly increased after contextual fear training compared to the control animals (Fig. 8.5). Interestingly, acetylation level decreased in SD-ELP animals after contextual fear training,

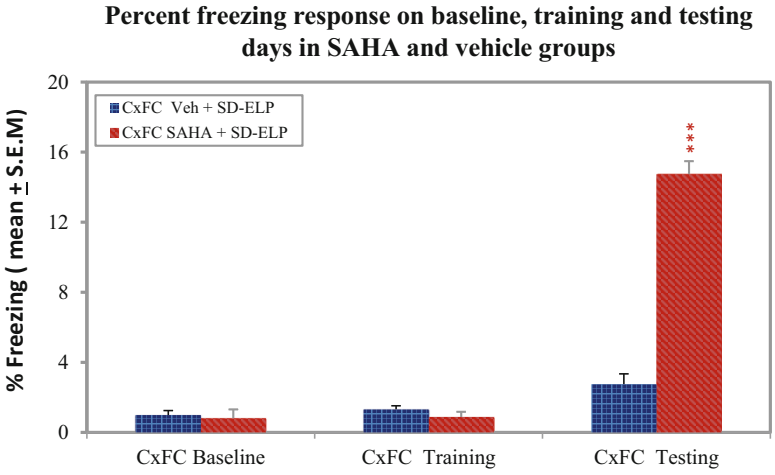

Fig. 8.4 Changes in % freezing response in SAHA + SD-ELP and vehicle + SD-ELP animals on baseline, training, and testing days. SAHA-treated animals exhibited significantly more freezing on testing day compared to baseline and training. The percent freezing response on baseline and training days was comparable in both group, but percent freezing response on testing day was significantly increased in SAHA + SD-ELP animals compared to vehicle + SD-ELP animals ($p < 0.001$, $F_{(1, 11)} = 156.612$) *** means $p < 0.001$ compared to CxFCVeh+SD-ELP group (*one-way ANOVA followed by Tukey* post hoc *test*). Abbreviations: *CxFC* contextual fear conditioning, *SD-ELP* sleep deprivation during extended light period (7:00 PM–1:00 AM). (Taken from G. Singh's PhD Thesis)

suggesting that sleep deprivation alters histone acetylation. SAHA microinjection in the dorsal hippocampus significantly increases H4K12 acetylation in normal and CxFC trained SD-ELP animals (Fig. 8.5). These results demonstrate that the sleep loss-mediated memory deficit can also be rescued by enhancing H4K12 histone acetylation.

8.4 Reactivation of Fear Memory During Sleep

Sleep possibly helps consolidate memories by facilitating the integration and strengthening of the neural circuitries (Diekelmann and Born 2010; Lewis and Durrant 2011; Rasch and Born 2013; Stickgold and Walker, 2013). Wilson and McNaughton (1994) have reported that the information acquired during acquisition is re-expressed in the hippocampal circuitry during sleep. They observed that some hippocampal place cells fired together when the animals explored a particular location in the environment. Interestingly, the cells which fired together during exploration exhibited an increased tendency to fire together during the subsequent sleep period (Wilson and McNaughton 1994). The *memory replay* during sleep might follow the same temporal order in which the cells fired during spatial exploration (Wilson and McNaughton 1994; Knierim 2009). Neuronal activity

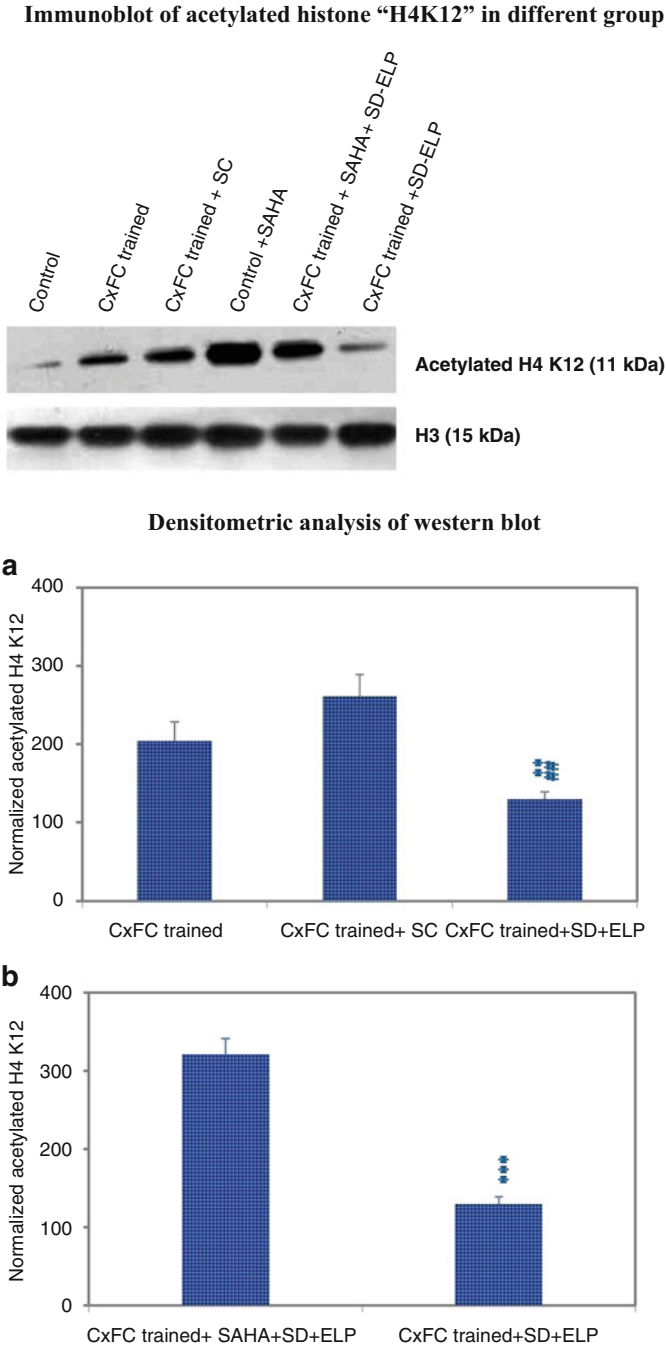

Fig. 8.5 Western blot and densitometric analysis of western blot showing the changes in acetylation of histone "H4K12" in different groups. The control animals (no CxFC) exhibited a lowest basal level of acetylation. The level of acetylated H4K12 increased in CxFC trained and CxFC trained stress control (CxFCtrained+SC) animals 6 h after training. Interestingly, it significantly decreased in CxFC trained sleep-deprived (CxFC+SD-ELP) animals after 6 h of sleep deprivation. In CxFC-training+SAHA-treated animals, level of acetylated H4K12 increased significantly, which also remained elevated in the CxFC trained sleep-deprived SAHA-treated animals (CxFCtrained+SAHA+SD-ELP). (Taken from G. Singh's PhD Thesis)

patterns observed during learning particularly in the hippocampus are replayed during sleep which seems to be an essential component of memory processing (Breton and Robertson 2013). The active system consolidation hypothesis posits that memory consolidation underlies the reactivation of the recently encoded memory representations (Rasch and Born 2013). In some human studies, sensory cues (auditory or olfactory) have been used to reactivate memories during the night, and it was observed that it robustly influenced memory strengthening during their subsequent recall (Rudoy et al. 2009; Antony et al. 2012).

8.5 Reactivation of Fear Memory During NREM Sleep

The spontaneous reactivation phenomena that have been shown to occur during NREM sleep mediates the transfer of temporarily stored information in the hippocampus to long-term storage sites (Lee and Wilson 2002). NREM sleep is characterized by events like sharp-wave ripples (SW-R) in the hippocampus along with slow neocortical and thalamic oscillations. The hippocampal SW-R plays an essential role in the consolidation of spatial memory. The disruption in the hippocampal SW-R activity during the post-learning period impairs memory, whereas, augmentation in neocortical slow-waves potentiates memory (Barnes and Wilson 2014). Sleep or sleep-like state is an ideal condition for memory consolidation because it helps in minimizing interference from external events as well as facilitates the flow of sensory information from the thalamus to the neocortex (Murakami et al. 2005). The re-exposure of the sensory stimuli associated with learning during NREM sleep can boost memory consolidation possibly by facilitating the effectiveness of repeated reactivations (Rasch et al. 2007). Nakashiba et al. have provided somewhat direct evidence regarding the facilitatory role of slow waves during NREM sleep in memory consolidation. They altered SW-R-associated reactivation of CA1 neurons by genetically blocking the hippocampal CA3 output. It was observed that SW-R reduction through genetic manipulation significantly impaired the consolidation of contextual fear memory (Nakashiba et al. 2009). A similar finding has been found in another study that re-exposure of the odor cues during NREM sleep in human subjects facilitated memory consolidation, whereas the re-exposure of the odor cue during REM sleep did not (Rasch et al. 2007). These reports clearly demonstrate that NREM sleep-associated events such as slow oscillatory activity, SW-R, sleep spindles, etc. facilitate neural reactivation during NREM sleep and thus contribute to memory stabilization (Cordi et al. 2014).

8.6 Reactivation of Fear Memory During REM Sleep

The experience-mediated neuronal activation during wakefulness also reoccurred in a similar way during REM sleep. Hennevin and his group have observed that neurons of the dorsal hippocampus and medial geniculate nucleus are highly

activated after cued fear conditioning. For fear conditioning, they have used tone as the conditioned stimulus paired with the unconditioned stimulus "foot shock." Following training, the non-awakening tone alone was represented during REM sleep. They observed that some neurons in the hippocampus and the auditory thalamus exhibited enhanced tone responsiveness during REM sleep (Hennevin et al. 1993). A similar study was carried out with multiunit recordings in the auditory thalamus and lateral amygdala. It was observed that the conditioned neural responses to fear largely increase in the lateral amygdala and medial geniculate nucleus during REM sleep. These results suggested that neurons involved in emotionally conditioned responses are capable of responding to the reinforcing stimuli during REM sleep (Hennevin et al. 1995).

Now, an intriguing question is, can the conditioned response be expressed during wake if the conditioning is performed during sleep? There is evidence suggesting that animals elicit conditioning response during the wake period when the animals are conditioned to lick behavior during sleep. This was ascertained by using the second-order conditioning protocol (Hennevin and Hars 1992). Animals were trained to lick-training along with low-level electro-tactile stimulation (ETS) to the ear during the alert condition. On the following day, the animals were exposed to second-order pairing with a tone signaling ETS delivery while they were either awake or asleep. Animals were subsequently tested for the acquisition of second-order association by monitoring lick-suppression response to the tone. It was reported that animals acquiring tone-ETS association during both, NREM and REM sleep, exhibited lick suppression to the tone while they were awake. In another similar study, Hennevin and colleagues (Hars et al. 1985) trained rats for active avoidance task, in which, an aversive foot shock (US) was associated either with a tone or a mild electrical shock to the ear (CS). During the post-learning period, the CS was redelivered to the rats during REM sleep episodes in the absence of US. Re-exposure of non-awakening ear shocks not only increased the duration of REM sleep but also significantly improved subsequent active avoidance performance (Hars et al. 1985). These results suggest that the paired external sensory stimuli presented either during NREM or REM sleep could induce conditioned behavioral response during wake.

Growing evidence undoubtedly suggest that memory reactivation induced by external cues during sleep evidently strengthened emotional memories. It is believed that neuronal activation occurs during both NREM and REM sleep, and sleep-stage-specific sleep components such as theta waves during REM sleep and delta waves during NREM sleep contribute to neuronal activation. Rats trained to shock avoidance learning showed increased theta power during REM sleep and subsequent increase in sleep spindles in NREM sleep (Fogel et al. 2009). On the other hand, a decrease in REM sleep theta power and increased delta power during NREM sleep were observed after fear conditioning (Hellman and Abel 2007). In addition, it has been found that synchronization of theta frequencies increases in the amygdalo-hippocampal network after fear conditioning (Seidenbecher et al. 2003). These studies suggest that sleep components are possibly enhancing the neuronal communication between different circuitries and inducing both, memory strengthening and memory stability.

8.7 The Role of Sleep in Fear Extinction

The conditioned fear responses can be weakened by a phenomenon called "fear extinction." Previously fear-conditioned animals/subjects, if repeatedly exposed to the conditioned context in the absence of any aversive stimulus, may weaken their negative conditioned memory (Myers et al. 2006). Fear extinction is not similar to forgetting; rather during the process, a new memory is formed where animals/subjects learn that the CS is not paired with the US, and thus the life-threatening feeling diminishes (Myers and Davis 2007). Extinction phenomena can be termed as "inhibitory learning," as a fear response is inhibited when the CS-US association is abolished (Quirk et al. 2010). It is well established that hippocampal-cortical circuits play a central role in the formation of CS representations, whereas CS-US associations are believed to be processed by the basolateral amygdala (Kim and Fanselow 1992; Phillips and LeDoux 1992; Debiec et al. 2010). It has also been shown that the PFC neurons are recruited during fear extinction, which inhibit the output regions of the amygdala and thereby reduce the fear response (Maren and Quirk 2004).

8.7.1 REM Sleep and Fear Extinction

REM sleep also plays an essential role in the consolidation of extinction memory. REM sleep-deprived animals exhibited normal retention of cued and contextual fear-conditioned memories but showed impairments in the extinction of cued fear memory (Silvestri 2005). Later, it was demonstrated more clearly that REM sleep deprivation impairs recall of the hippocampal-independent fear extinction memory, but not the hippocampal-dependent fear extinction memory (Fu et al. 2007). Interestingly, 6-h REM sleep deprivation immediately after training significantly altered extinction memory, but REM sleep deprivation 6 h after training had no effect (Fu et al. 2007). These results provide evidence that REM sleep may be playing a crucial role in the consolidation of extinction memory.

REM sleep deprivation possibly alters NMDA receptor sensitivity and/or its associated events, which may be involved in extinction memory. Administration of NMDA receptor agonist "d-cycloserine" to REM sleep-deprived animals partially reversed extinction memory deficit, suggesting that REM sleep deprivation-mediated effects on extinction memory could be partially mediated through the NMDA-dependent mechanisms (Silvestri and Root 2008). In addition, potentiation of phasic P-wave activity in the brainstem during post-training REM sleep plays a crucial role in the consolidation of fear extinction memory. It has been proposed that post-training increased sleep amount alone may not be enough to retain the fear extinction memory; the augmented sleep-associated events can also play a crucial role in memory consolidation (Datta and O'Malley 2013).

8.8 Fear Memory Interference During Sleep

The neural replay during sleep contributes to memory strengthening (Abel et al. 2013). It has been shown that *targeted memory reactivation* strengthens memories (Rasch et al. 2007; Rudoy et al. 2009; Antony et al. 2012), but it is not yet known if the same targeted memory reactivation tool can be used to weaken negative memories. Two recent studies in rats and humans have used this approach to abolish negative memories. Rolls and group (2013) have conditioned mice to fear, during which the foot shocks (US) were delivered in the presence of an odor. Twenty-four hours later, the CS odor was again presented during sleep. They observed an increased freezing response during wakefulness. Thereafter, they bilaterally injected protein synthesis inhibitor specifically into the basolateral amygdala before re-exposing the CS odor during sleep. Interestingly, blocking new protein synthesis during targeted memory reactivation led to a decline in the fear response on the following day. These findings suggest that interference in the reactivation processes of targeted fear memory during sleep can also cause memory deficit.

Furthermore, Hauner and colleagues conditioned 15 healthy humans differently (Hauner et al. 2013). All the volunteers underwent olfactory contextual conditioning. The images of different faces as CS were shown to them. Every image was paired with a neutral smell such as lemon or mint, but some of them were paired with mild electrical shock (US). The conditioning procedure was performed inside a fMRI scanner, and the skin conductance response (SCR) and the amygdala and hippocampal activities were monitored. Following conditioning, volunteers were allowed to sleep for about 70 min outside the scanner. During the nap time, the participants were re-exposed to one of the smells they had earlier experienced during the conditioning. It was observed that odor re-exposure gradually diminished the fear response, as measured by the changes in SCR and fMRI. When the subjects woke up, same face images were shown to them. Projection of the face images elicited fearful responses only with those images to which the corresponding odor was re-exposed during sleep. In addition, they observed that the amygdalar activity associated with fear extinction during sleep was entirely different from that observed at the time of conditioning. These findings suggest that the extinction of fear memory can be accomplished without having a conscious perception of the re-exposed context.

In another study, the role of sleep in the consolidation of fear extinction memory has been demonstrated (He et al. 2015). In their study, humans were subjected to cued fear conditioning, and an increase in skin conductance response to the conditioned stimulus was considered as an outcome measure of fear. All subjects were allowed to sleep for 4 h. During NREM sleep, volunteers were repeatedly re-exposed to the tone, which led to a decrease in the subsequent fear response, as compared to subjects who were either exposed to a different tone during NREM sleep or no tone at all. These studies support the view that presenting cues during sleep indeed gradually attenuates fear responses as well.

8.9 The Consolidation of Fear Memory Requires NREM Sleep

Within sleep, the proportion of NREM sleep significantly increases after the consolidation of fear memory, and sleep architecture does not change if memory is impaired (Kumar and Jha 2017). Further, REM sleep significantly decreases after the consolidation of fear memory, but REM sleep does not change if the consolidation of fearful memory processes is altered (Kumar and Jha 2017). These findings suggest that there could be a high probability of augmentation of NREM sleep after fear conditioning, and it could be associated with the consolidation of fearful memory. To demonstrate this, we have taken two independent approaches: (i) the expression of NREM and REM sleep were correlated with the amount of freezing response, and (ii) the Bayesian rule was applied to predict if there is a high probability of NREM sleep augmentation after successful consolidation of fear memory, and low probability of NREM sleep augmentation after fear memory was impaired.

8.9.1 The Expression Ratio of NREM/REM Sleep Correlates with the Freezing Response

The expression ratio of NREM/REM sleep significantly correlates with the freezing response in consolidated memory group, while it did not correlate in memory-impaired group (Fig. 8.6). We performed Pearson correlation test between NREM/REM ratio (out of sleep time) and percent freezing amount on the training and testing days. It was observed that NREM/REM ratio (out of total sleep time) did not correlate with percent freezing response on the training day ($r = 0.14$, $p = 0.28$). While, on the testing day, NREM/REM ratio significantly positively correlated with percent freezing response ($r = 0.36$, $p < 0.01$) (Fig. 8.6). On the other hand, the expression ratio of NREM/REM sleep did not significantly correlate in the memory-impaired group. A significant positive correlation between NREM/REM ratio and freezing response in the consolidated memory group suggests that the consolidation of fear memory is sleep-dependent.

8.9.2 The Bayesian Predictions for the Probability of NREM Sleep Augmentation in Memory-Consolidated and Impaired Groups

Bayesian probabilistic model is one of the popular approaches used increasingly to understand learning and cognition (Jacobs and Kruschke 2011; Shankle et al. 2013). We have used the Bayesian rule to predict if there is (a) a high probability of NREM

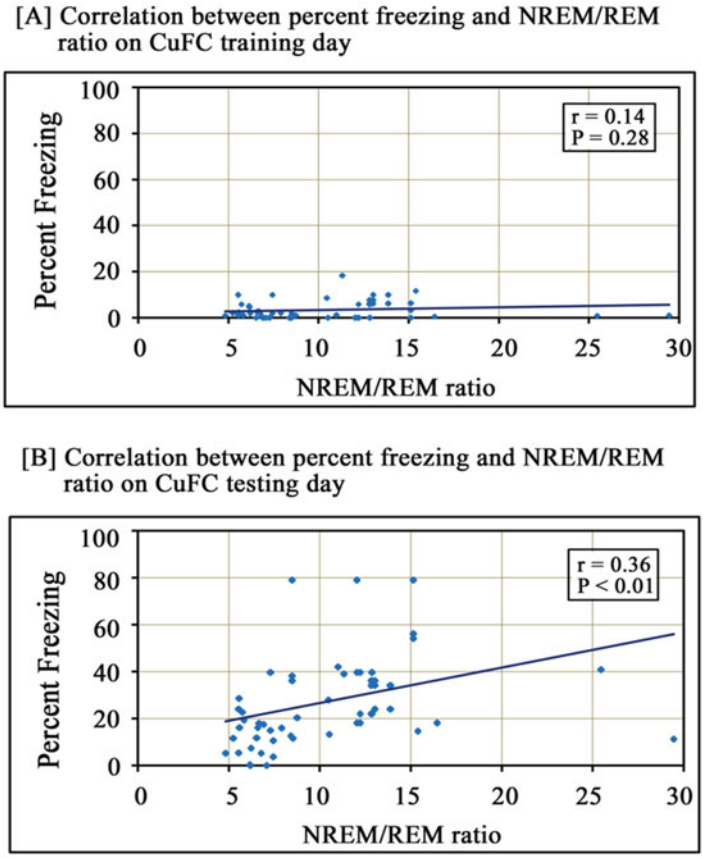

Fig. 8.6 Correlation between percent freezing response and NREM/REM ratio (out of total sleep time) ($n = 64$) on CuFC training and testing days. (**a**) NREM/REM ratio did not correlate with percent freezing response on the CuFC training day ($r = 0.14$; $p = 0.28$). (**b**) On the CuFC testing day, NREM/REM ratio significantly positively correlated with percent freezing response ($r = 0.36$, $p < 0.01$) in the memory-consolidated group. Abbreviations: *CuFC* cued fear conditioning. (Taken from T Kumar's PhD Thesis)

sleep augmentation after CuFC memory was consolidated and (b) a low probability of NREM sleep augmentation after CuFC memory was impaired (pharmacologically). Animals which demonstrated successful cued fear conditioning ($n = 41$) were placed in the memory-consolidated (MC) groups. On the other hand, we pharmacologically altered cued fear conditioning in 23 animals and placed them in memory-impaired (MI) group. We recorded sleep in all animals before and after conditioning and changes in NREM and REM sleep amount on the conditioning day were compared with before conditioning day. We found that REM sleep significantly decreased, but NREM sleep significantly increased out of total sleep time in a memory-consolidated group on the conditioning day. Statistically significant or nonsignificant increase in NREM sleep after CuFC training was determined in

Table 8.1 Number of animals divided into four groups in the Bayesian table

	MC	MI	Total
$NREM^{(inc)}$	31	2	33
$NREM^{(no\text{-}inc)}$	10	21	31
Total	41	23	64

$NREM^{(inc)}$= NREM sleep significantly increased
$NREM^{(no\text{-}inc)}$= NREM sleep did not increase
MC = Memory consolidated
MI = Memory impaired
Taken from Tankesh's PhD Thesis

each animal by computing mean of hourly NREM sleep and was compared with the baseline of the same animal using one-way RM-ANOVA followed by Tukey post hoc test. The animals were then accordingly assigned to any of the four groups: Group I, significant increase in % NREM sleep ($NREM^{inc}$) in MC group; Group II, nonsignificant changes in % NREM sleep ($NREM^{no\text{-}inc}$) in MC group; Group III, nonsignificant changes in % NREM sleep ($NREM^{no\text{-}inc}$) in MI group; and Group IV, significant changes in % NREM sleep ($NREM^{inc}$) in MI group (Table 8.1).

We found that out of total 41 animals in the memory-consolidated group, NREM sleep significantly increased in 31 animals, while it did not change in 10 animals. Accordingly, we placed them in the memory-consolidated group but under increased or no change in NREM sleep groups. Similarly, in 23 animals in the memory-impaired group, 2 animals showed significantly increased NREM sleep, but 21 animals showed no change in NREM sleep. Hence, we placed them in memory-impaired but under increased or no change in NREM sleep group, respectively (Table 8.1).

We applied 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 cued fear memory was impaired.

Bayes' formula:

$$P(A/B) = \frac{P(B/A) \times P(A)}{P(B/A) \times P(A) + P(B/A) \times P(B)}$$

where $P(A)$ is the probability of event A; $P(B)$ is the probability of event B; $P(A/B)$ is the probability of event A when B is present; and $P(B/A)$ is the probability of event B when A is present.

(i) **The probability for NREM Sleep augmentation after CuFC memory consolidation:**

$$P\left(\mathrm{MC}/\mathrm{NREM}^{(\mathrm{inc})}\right) = \frac{P\left(\mathrm{NREM}^{(\mathrm{inc})}/\mathrm{MC}\right) \times P(\mathrm{MC})}{P\left(\mathrm{NREM}^{(\mathrm{inc})}/\mathrm{MC}\right) \times P(\mathrm{MC}) + P\left(\mathrm{NREM}^{(\mathrm{inc})}/\mathrm{MI}\right) \times P(\mathrm{MI})}$$

$$P\left(\mathrm{MC}/\mathrm{NREM}^{(\mathrm{inc})}\right) = \frac{\frac{31}{41} \times \frac{41}{64}}{\frac{31}{41} \times \frac{41}{64} + \frac{2}{23} \times \frac{23}{64}}$$

$$P\left(\mathrm{MC}/\mathrm{NREM}^{(\mathrm{inc})}\right) = \frac{0.48}{0.48 + 0.03} = 0.94$$

The high predictive value 0.94 suggests that there is a high probability of NREM sleep augmentation after CuFC memory consolidation.

(ii) **The probability for NREM Sleep augmentation after CuFC memory impairment:**

$$P\left(\mathrm{MI}/\mathrm{NREM}^{(\mathrm{inc})}\right) = \frac{P\left(\mathrm{NREM}^{(\mathrm{inc})}/\mathrm{MI}\right) \times P(\mathrm{MI})}{P\left(\mathrm{NREM}^{(\mathrm{inc})}/\mathrm{MI}\right) \times P(\mathrm{MI}) + P\left(\mathrm{NREM}^{(\mathrm{inc})}/\mathrm{MC}\right) \times P(\mathrm{MC})}$$

$$P\left(\mathrm{MI}/\mathrm{NREM}^{(\mathrm{inc})}\right) = \frac{\frac{2}{23} \times \frac{23}{64}}{\frac{2}{23} \times \frac{23}{64} + \frac{31}{41} \times \frac{41}{64}}$$

$$P\left(\mathrm{MC}/\mathrm{NREM}^{(\mathrm{inc})}\right) = \frac{0.03}{0.03 + 0.48} = 0.06$$

A minimal predictive value 0.06 suggests that there is no probability of NREM sleep augmentation after CuFC memory impairment.

The Bayes' rule clearly demonstrated that there is a high probability of NREM sleep augmentation after the consolidation of CuFC memory and low probability for NREM sleep augmentation after memory impairment. It further suggests that the consolidation of CuFC memory requires NREM sleep for memory consolidation.

8.10 Conclusions

It has been widely discussed globally since years to find out how can bad/negative memories could be erased in humans. Our findings, that post-learning NREM sleep facilitates fear memory, suggest that short-term sleep deprivation soon after experiencing traumatic events could potentially be used to prevent the consolidation of negative memories. It, however, needs further study mainly on human subjects before the approach is adapted for therapeutic use.

Further, we have found that REM sleep is decreased after fear conditioning, which may play the role of a negative modulator for the consolidation of fear memory. Our results show that decreased REM sleep after fear conditioning could be an obligatory phenomenon for the consolidation of fear memory. It thus suggests that the development and use of REM sleep inducing drugs can be used as potential

treatments to erase negative or traumatic memories soon after experiencing traumatic events.

Finally, our results also show that sleep modulates epigenetic regulation of gene expression underlying consolidation of contextual fear memory. Similar to cancer therapy, drugs which can alter histone acetylation at epigenetic level can possibly be used as a therapeutic measure to counteract the development of anxiety disorders such as PTSD in humans.

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Chapter 9
Sleep and Appetitive Conditioned Memory

Shweta Tripathi, Shweta Tripathi, Anjali, and Sushil K. Jha

Abstract In associative appetitive learning, an individual learns to extract logical information of the conditioned stimulus to predict the potential outcomes. How the conditioned stimulus drives appropriate predictive behavior is not yet known, but it has been found that the association is formed at neural level between the conditioned and unconditioned circuitries. The conditioned stimulus possibly generates many different types of associations with the appetitive unconditioned stimulus. For example, the conditioned stimulus forms an association with food (unconditioned stimulus) through their specific (i) affective and (ii) preparative properties. These properties may be encoded and represented at different neural circuitries in different brain regions. Several neurotransmitters, such as dopamine, glutamate, serotonin, cannabinoids, and opioids, play an important role in appetitive conditioning. Some neuropeptides such as orexin, leptin, ghrelin, etc. are also involved in the modulation of the affective attribute of appetitive conditioning tasks. In addition, a large number of studies consistently revealed the role of sleep in a variety of learning tasks such as declarative memory, procedural memory, and spatial learning tasks. The role of sleep in appetitive conditioning tasks has, however, not been investigated in detail. We have reported that short-term sleep deprivation soon after training impairs the consolidation of appetitive conditioned memory. We have also found that the consolidation of appetitive conditioned memory requires augmented REM sleep after training. In this chapter, we have discussed in detail the role of different brain areas, neural circuitries, and, more specifically, sleep in appetitive conditioning.

Keywords Appetitive Conditioning · SWA · Learning · NREM sleep · REM sleep · Sigma Waves · Theta Waves

Shweta Tripathi is the name of two contributors of this chapter having exactly same name & affiliation.

S. Tripathi · S. Tripathi · Anjali · S. K. Jha (✉)
Sleep Research Laboratory, School of Life Sciences, Jawaharlal Nehru University, New Delhi, India
e-mail: sushilkjha@mail.jnu.ac.in

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9.1 Introduction

The changes in sleep architecture after learning different training tasks suggest that discrete memory types may require augmentation of specific sleep stages, either non-rapid eye movement (NREM) or rapid eye movement (REM) sleep or both for memory strengthening. Many studies have shown that NREM sleep amount, slow-wave activity, and sleep spindle density during NREM sleep increased after learning associative and skill-related tasks (Eschenko et al. 2006; Hanlon et al. 2009; Hellman and Abel 2007; Kumar and Jha 2012, 2017). It has been also reported that REM sleep increases exclusively after learning spatial learning tasks, negative and positive reinforcement tasks, avoidance tasks, and aversive and appetitive conditioning tasks (Fishbein 1971; Fishbein and Gutwein 1977; Hanlon et al. 2005; Hayes et al. 2014; Kennedy 2002; Morris et al. 1982; Walker and Stickgold 2004).

The evidence in support of the role of sleep in memory consolidation can also be obtained through sleep deprivation. William C. Dement and his group, in his study in 1965, have shown that REM sleep-deprived animals exhibited reduced threshold for an electroconvulsive shock (Cohen and Dement 1965). Further, several studies using various animal models such as the rat, mouse, cat, etc. have demonstrated that REM sleep deprivation alters specifically hippocampal-dependent tasks, for example, appetitive reinforcement task, spatial learning task, etc. (Cohen et al. 1967; Colavito et al. 2013; Kennedy 2002; Walker and Stickgold 2004; Walsh et al. 2011; Yang et al. 2008). REM sleep deprivation, continuously for 96 h, significantly altered appetitive reinforcement response in the rat but not the motivation associated with food reward (Kennedy 2002). In some other studies, it has, however, been found that sleep deprivation can alter the motivation to obtain food or other reinforcer associated with the task (Hanlon et al. 2005). Prolonged sleep alteration grossly affects appetitive behavior. The body weight of laboratory animals more often decreases with prolonged sleep deprivation (NREM as well as REM sleep deprivation) despite an increase in a regular food intake during the deprivation period (Everson et al. 1989; Kushida et al. 1989). In 1991, Mahowald and his group observed for the first time, a sleep-related eating disorder in some parasomniac patients (Schenck et al. 1991). These patients exhibited nightly eating behavior while they were sleeping. Interestingly, these patients demonstrated no recollection or some partial recall of their eating episodes. None of the patients complained of hunger, thirst, or initial insomnia before going to bed (Schenck et al. 1991). These studies suggest that sleep alteration or fragmentation may have a substantial impact on appetitive behavior.

Further, some epidemiologic studies have demonstrated a close link between chronic sleep loss and changes in basal metabolic rate (for review see Knutson and Van Cauter 2008). The energy status of the body is primarily maintained by the hypothalamus through a hormone *leptin*, which is released by the adipocytes (Ahima et al. 2000). The acute caloric shortage or surplus influences the levels of circulating leptin in humans (Ahima et al. 2000). In one of the interesting studies, Morselli et al. (2010) have demonstrated that total sleep deprivation alters the level of circulating leptin (Morselli et al. 2010). Since 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 (Mullington et al. 2003). Another hormone *ghrelin*, produced predominantly by the stomach, is also involved in the regulation of energy balance. 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 to maintain a balance of our meal consumption. Interestingly, it has been observed in humans that sleep deprivation induces subjective hunger (Schmid et al. 2007) and alters the level of leptin, suggesting that sleep and appetitive behavior are closely linked.

In animals, foraging-associated appetitive behavior is learned through experiences as well as through social learning (Mazur and Seher 2008). Quick learning to discriminate between conducive and hostile environment for foraging helps the animals to survive successfully (Belguermi et al. 2011). Animals learn to discriminate between safe and unsafe conditions through the stable individual cues and context of the environment, and it ultimately helps them to judge whether to approach for food or stay away (Belguermi et al. 2011). Associative learning thus allows the organisms to extract logical information from the associative stimuli so that they can predict the potential outcome. Therefore, an efficient appetitive conditioned learning becomes crucial for the survival of the organism.

An organism's ability to evaluate its surrounding is essential and for its well-being and survival under natural habitat. Behavioral data have shown that an animal has to pay different amount of attention to these stimuli, which involves different neuromodulatory systems (Dayan et al. 2000). The evaluation processes require a dynamic assessment of outcomes of the positive and negative stimuli, which an organism has to encounter in its environment. This type of value-related processing of stimuli in humans and other animal models reflects the activity of aversion and/or appetitive-linked brain areas (Hayes et al. 2014; Hayes and Northoff 2011; McBride et al. 1999; O'Doherty 2004). Studies related to the role of sleep and associated neuro-circuitries have so far mainly used the classical aversive conditioning paradigm. The role of sleep in the consolidation of appetitive conditioned memory has, however, not been studied in detail. In this chapter, we discuss some salient features of factors affecting appetitive conditioning behavior. Further, we have also attempted to review the role of few individual brain areas involved in appetitive conditioning and how sleep performs a crucial role in the consolidation of appetitive conditioned memory.

9.2 Appetitive Conditioning

Appetitive conditioning is one of the examples of classical conditioning, in which, the conditioned stimulus (CS) acquires the motivational salience from food (Martin-Soelch et al. 2007). In appetitive conditioning, a neutral stimulus (NS), such as tone/light, is repeatedly presented along with food or fruit juice as unconditioned stimulus (US) (Chowdhury et al. 2011; Tripathi and Jha 2016). Due to the repeated presentation of the CS with the US, the CS, with time, gradually acquires the properties to

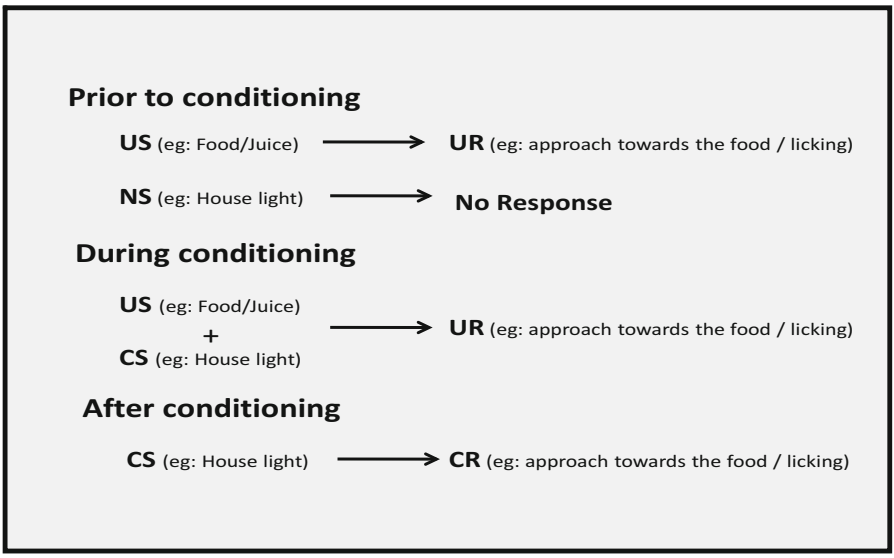

Fig. 9.1 Events associated with appetitive conditioning: Association of the CS and US during classical appetitive conditioning task. Prior to conditioning, the CS does not induce any response, but after repeated presentations of the CS along with the US, the CS gains properties to induce conditioned responses. *Abbreviations*: *US* unconditioned stimulus, *NS* neutral stimulus, *UR* unconditioned response, *CS* conditioned stimulus, *CR* conditioned response

trigger almost same motivational reactions, which are exclusively induced by the US. In other words, the CS induces conditioned responses (CR) that were initially generated by the US only (Fig. 9.1).

One of the main requisites for classical conditioning is that the US should elicit an innate reflex called the unconditioned reaction (UR), which occurs primarily at a physiological level. For the successful conditioning, it is important that the US and CS must be presented temporally in a paired fashion or in a close proximity (Pavlov (1927) 2010). It enables the subjects to predict the occurrence of the US-mediated events after facing the CS (Hamm and Vaitl 1996). Since appetitive conditioning involves the presentation of two paired stimuli, the CS and US, such associative learning initiates strong stimulus-stimulus connections between the stimuli. Appetitive conditioning experiments have been performed in various animal models, and it has been found across species that the CS acquires the representation of the US, if repeatedly presented in a paired fashion (Pearce and Bouton 2001).

9.2.1 Types of Appetitive Conditioning

The nature of conditioning primarily depends on the manner, in which, the conditioned stimulus (CS) and the unconditioned stimulus (US) appear during the trials

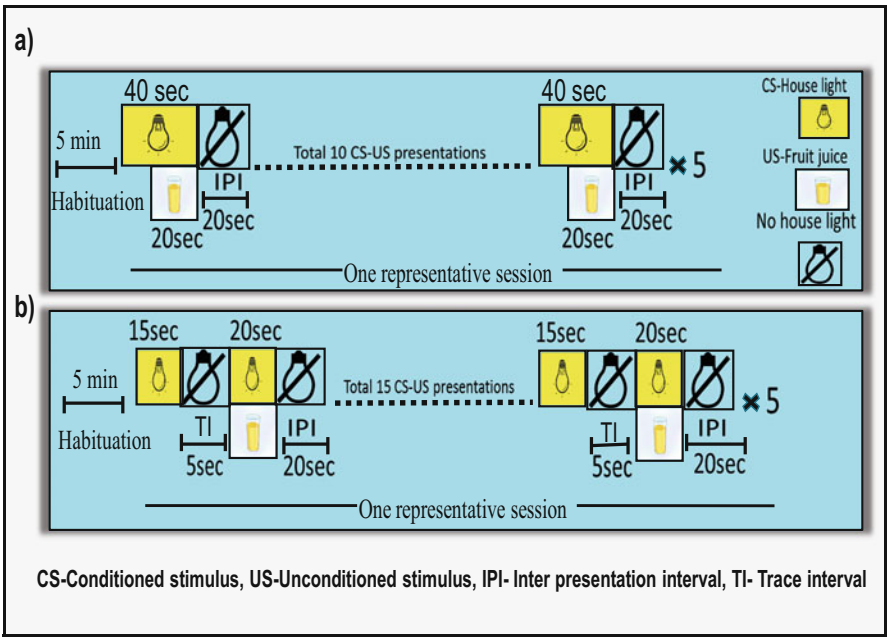

Fig. 9.2 Diagrammatic representation of (**a**) delay and (**b**) trace appetitive conditioning protocols. In delay conditioning, house light as the CS (presentation period, 40 s) is paired with fruit juice as the US (presentation period, 20 s), and both terminate together. While in trace conditioning, the CS (house light) and the US (fruit juice) are presented for 15 and 20 s, respectively, at a 5 s trace interval. *CS* conditioned stimulus, *US* unconditioned stimulus, *IPI* inter-presentation interval, *TI* trace interval

(Chowdhury et al. 2011). For example, delay and trace conditioning are two distinct examples of classical conditioning. In delay conditioning, CS and US both terminate at the same time point, while in trace conditioning, a silent period elapses between the offset and onset of the CS and US (Fig. 9.2) (Chowdhury et al. 2011). The two important components, which play an important role in learning the associative task, are the retrieval of information of temporal events and context. The time, when an event occurs, is important for effective learning, but another crucial factor is the duration of the entire learning episode. Differences in the protocol of these two conditioning paradigms appear simple, but the actual effect on the learning processes is profound. For example, (i) trace conditioning requires more number of presentation of the CS and US paired stimuli for conditioning than the delay conditioning (Beylin et al. 2001); (ii) trace-conditioned memory is hippocampus-dependent, while delay-conditioned memory can be encoded without the hippocampus (Rodriguez and Levy 2001; Woodruff-Pak and Disterhoft 2008); and (iii) the neural circuitries underlying delay conditioning appear to be strong and remain intact even in the old age and ailing subjects, whereas the circuitries involved in trace conditioning decline with aging and during pathological conditions (Gabrieli et al. 1995; Graves and Solomon 1985; Grillon et al. 2007; Solomon and Graves 1985).

9.3 Different Animal Models Used to Study the Appetitive Conditioning

Exploring the neurobiology of the prediction of appetitive events has long been a major focus of neuroscience research, but appetitive conditioning has not been investigated in detail. Only a few studies have been done on humans (Cox et al. 2005; De Houwer et al. 2001), rats, mice, and monkeys (Hayes et al. 2014). Some studies on reward processing have also been conducted in invertebrate animal models such as crickets, honeybees, etc. (Barron et al. 2002, 2010; Matsumoto et al. 2012; Mizunami and Matsumoto 2010). Besides these, the appetitive conditioning studies have been performed in *Lymnaea* (Staras et al. 1999) and *Aplysia* (Baxter and Byrne 2006). Further, the role of an integrated neural system of the amygdala and orbital prefrontal cortex in decision-making and adaptive response selection has been studied in the monkey (Baxter et al. 2000). Animals with surgically disconnected amygdala and orbitofrontal cortices along with forebrain commissurotomy showed a reduction in the value of a specific reinforcer and impairment in their choice behavior. However, the motivation toward food reinforcer or food preferences remained intact (Baxter et al. 2000). It has also been observed that the same neuron of dorsal raphe nucleus (DRN) encodes for both appetitive and aversive information (Hayashi et al. 2015). Hayashi et al. (2015) have trained the monkeys for trace conditioning using two distinct tasks, (a) appetitive task and (b) aversive task, and have investigated how DRN neurons encode the expectation of appetitive (rewards) and aversive (air puffs) stimuli. In their interesting study, they observed that the same neuron in the DRN computes both appetitive and aversive information probably through the dual firing patterns, a tonic firing to discriminate emotional contexts and a relatively phasic or quantitative firing to encode rewarding events (Hayashi et al. 2015).

To broaden the appetitive conditioning experiments in other animal models, Longo et al. (1964) had performed the conditioning task in pigeon (Longo et al. 1964). They found that the 10 s CS-US interval yielded better conditioning results than the 1 s interval (Longo et al. 1964). Nevertheless, similar differential response was not observed in fish with varying CS-US time interval (Behrend and Bitterman 1964). The classical olfactory conditioned response in the honey bee involving the proboscis extension response (PER) is a well-established model of learning and memory in insects (Takeda 1961). It is a reflexive response, which is induced when tarsi come in direct contact with sucrose solution. In response, the bee extends its proboscis to drink the sucrose solution. During conditioning, when an odor is presented repeatedly along with the sucrose solution, then the odor alone elicits the PER (Matsumoto et al. 2012; Takeda 1961). Studies on olfactory learning in insects have suggested that octopaminergic and dopaminergic signaling play an important role in conveying reinforcing signals (Mizunami and Matsumoto 2010). It has been proposed in the insect model of learning and memory that conditioning reinforces two types of synaptic connections: (i) neuronal connections between the neurons representing the conditioned stimulus and conditioned responses and (ii) the

connections between the neurons representing the conditioned stimulus and the octopaminergic and dopaminergic neurons representing appetitive unconditioned stimulus (Mizunami and Matsumoto 2010; Mizunami et al. 2009).

Among invertebrates, appetitive conditioning has also been performed in aquatic snails such as aplysia and lymnaea. Appetitive conditioning in aplysia is conducted by delivering paired presentations of tactile stimulation as conditioned stimulus along with seaweed food as the unconditioned stimulus (Baxter et al. 2000). The effect of the appetitive stimulus is assessed by counting the number of bites in response to the conditioned stimulus. In *Lymnaea*, Staras et al. (1999) have used tactile stimulation as conditioned stimulus paired with sucrose solution as an unconditioned stimulus. Their findings suggest that the electrophysiological correlates of learning can be recorded at multiple sites within the feeding network (Staras et al. 1999). In another study, Straub et al. (2004) used amyl acetate as the conditioned stimulus paired with sucrose solution as an unconditioned stimulus for one-trial appetitive conditioning (Straub et al. 2004). They have observed, however, that chemical appetitive conditioning affects only the central but not the peripheral chemosensory system (Straub et al. 2004). The studies on appetitive conditioning in different animal models have thus helped us to establish the best suitable and simple models to find out the neurobehavioral aspects of appetitive conditioning and also have provided the answer to "how the association of CS and US events takes place at the cellular and molecular level in the brain?".

9.4 Neural Circuitries and Neurotransmitters Associated with Appetitive Conditioning

The conditioning of appetitive learning may involve multi-level processes at different neural circuitries. The conditioned stimulus possibly generates many different types of associations with the unconditioned stimulus. For example, the conditioned stimulus forms an association with the unconditioned stimulus with their specific (i) affective and (ii) preparative properties (Martin-Soelch et al. 2007). These properties may be encoded and represented at different neural circuitries in different brain regions (Fig. 9.3).

Using electrophysiological and neurobehavioral methodologies, the neural bases of appetitive conditioning have been investigated in different animal models such as monkeys, rodents, cats, pigeon, honeybee, lymnaea, aplysia, etc. (Baxter and Byrne 2006; Baxter et al. 2000; Burns et al. 1993; Robledo et al. 1996). It has been observed in drosophila that some dopaminergic neurons convey the information of aversive stimulus, while octopaminergic (OA) neurons communicate the information of appetitive stimulus to the neurons of the mushroom body (Busto et al. 2010). The dopaminergic system also plays an important role in the enhancement of instinctive behavior and appetitive drives in animals, which eventually helps in forming the reward-seeking behavior and developing search strategies to obtain

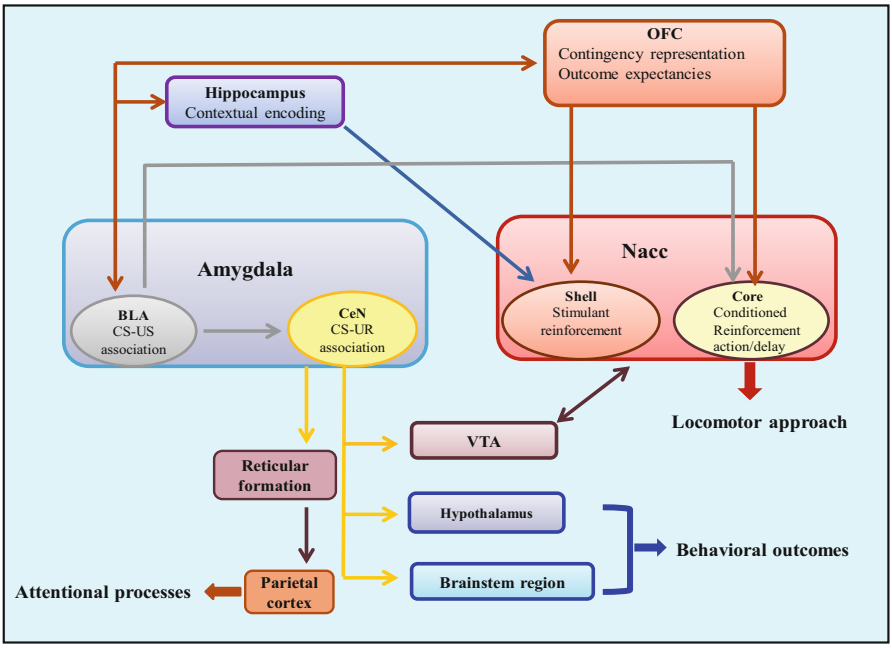

Fig. 9.3 The role of different brain areas in inducing neuronal and behavioral responses such as CS-US association, CS-UR association, locomotor approach behavior, attentional processes, etc.

the ultimate goal. The ventral tegmental area (VTA) of the midbrain, the primary dopaminergic nucleus, sends diffuse projections to various brain areas including the nucleus accumbens (NAcc) and prefrontal cortex (PFC) (Alcaro et al. 2007). In humans, neuroimaging techniques have been used to examine the neural correlates of appetitive conditioning (Gottfried et al. 2002; Martin-Soelch et al. 2007). These studies suggest that the neural network including the amygdala, hippocampus, nucleus accumbens, anterior cingulate cortex, orbitofrontal cortex, and the mesolimbic dopamine systems play an important role in appetitive conditioning (Passetti et al. 2000; Schoenbaum et al. 2003a, b).

9.5 The Amygdala

Studies suggest that the amygdalar complex plays an essential role in appetitive conditioning. It is implicated in assigning the emotional and attentional significance of events associated with appetitive conditioning. It has been observed that the amygdala lesion in rats, both before and after training of conditioned associative learning, resulted in impairment of emotional expression without any sensory-motor deficits (Ono et al. 1995; Phelps and LeDoux 2005). Therefore, it seems that the amygdala is involved in the processing of the information associated with emotional attributes of the stimulus. It

is also known that the amygdala relocates the information of the stimulus-affect association to the brainstem executing systems (Pearce and Bouton 2001). Various studies have shown that the different amygdalar nuclei, particularly the basolateral (BLA) and the central nucleus (CeN), serve as different sub-systems and are involved in distinct aspects of the conditioned learning (Martin-Soelch et al. 2007). For example, Gallagher et al. (1990) have shown that the CeN-lesioned animals showed substantial impairment in the acquisition of conditioned orienting responses but no deficit in acquisition of US-related behaviors (Gallagher et al. 1990). The acquisition of conditioned information was, however, impaired in rats with BLA lesions but not in rats with CeN lesions (Hatfield et al. 1996). Hence, it has been proposed that the BLA, but not CeN, is part of a system involved in the acquisition of CS-associated positive-incentive value (Hatfield et al. 1996).

(a) *Basolateral Amygdala (BLA)*

The basolateral amygdala has been found to be associated with the representation of values of outcomes, such as tasty food reward or an aversive foot shock. The involvement of BLA neurons in the representation of both fear and safety (Hobin et al. 2003; Sangha et al. 2013), as well as encoding of the value in appetitive and aversive outcomes, has been observed (Paton et al. 2006). It has also been noted in several anatomical, electrophysiological, and behavioral studies that the BLA associates sensory representations and their behavioral outcomes (Gore et al. 2015). The BLA neurons possibly mediate the acquisition of positive and negative associative memories as it has been found that the BLA projections to the NAcc and CeN induce opposing synaptic changes following fear or reward conditioning. The projections toward the NAcc mediate positive reinforcement, while projections toward the CeN mediate negative reinforcement (Namburi et al. 2015).

(b) *Central Nucleus of Amygdala (CeN)*

Although the BLA plays a significant role in appetitive conditioning, some studies have, however, indicated that the CeN could also be involved in the modulation of some attributes of appetitive conditioning. It has been observed that the CeN modulates the conditioned stimulus-mediated orienting response for food (Gallagher et al. 1990; Hatfield et al. 1996). The projections from the CeN to the dorsolateral striatum via the dopaminergic substantia nigra are involved in the conditioned orienting response in the rat (Han et al. 1997).

Furthermore, the conditioned locomotor approach in the autoshaping task is CeN-dependent (Everitt et al. 2003). In this task, the two different visual stimuli, as the CS, are presented on a computer screen. The presentation of one of the CSs is always accompanied with food delivery but at a different location, while no food is offered along with the presentation of another CS. The animal exhibits the CR by selectively approaching the CS predictive of food, and interestingly, it has been found that the CeN but not BLA lesions impair acquisition of autoshaping-mediated conditioned locomotor behavior (Parkinson et al. 2000a). Similar to the conditioned orienting response, the conditioned locomotor response also requires the dopaminergic innervation to the nucleus accumbens, which is primarily regulated by the CeN neurons (Parkinson et al. 2000a). These studies suggest that the CeN neurons also play an important role in the processing of some attributes of conditioned responses.

9.6 The Hippocampus

Although it is believed that the hippocampus does not have any direct role in the modulation of basic motivational processes, few studies suggest that selective hippocampus lesioning alters appetitive behavior. An increased number of food contacts along with increased eating frequency (Clifton et al. 1998; Davidson and Jarrard 1993), preservation of conditioned response even in the absence of reinforcer (Flaherty et al. 1998), and an increase in behavioral activity in the food-associated environment (Benoit et al. 1999) are some of the changes found to be directly associated with the hippocampus lesion. The hippocampal-lesioned animals, when food deprived, demonstrate an impairment in discriminating the food deprivation-mediated sensory consequences and satiation (Davidson and Jarrard 1993). These studies suggest that besides playing an important role in learning and memory, the hippocampus may also be involved in the processing of some intrinsic signals of food intake.

The hippocampus plays an important role in appetitive place conditioning (Ito et al. 2005, 2006). The intact hippocampus animals exhibited a strong preference to the place paired with food, but hippocampus-lesioned animals demonstrated impairment in exhibiting a significant preference (Ito et al. 2006). It has further been proposed that the two brain areas, hippocampus and basolateral amygdala, along with the dopaminergic afferent pathways to the nucleus accumbens complement each other to obtain control over goal-directed behavior (Ito et al. 2006).

9.7 The Nucleus Accumbens

Formation of association between predictive environmental events and their rewarding outcome is a fundamental requirement of learned behavior, which requires a complex neural processing to identify, seek, and utilize natural reward. Nucleus accumbens (NAcc) is an integral part of this circuitry and has been found to be associated with several reward-related behavioral training tasks. NAcc provides information of specific reward availability, its value, and other context-related details. For Pavlovian stimulus-reward relationships, this region plays a role in acquisition and expression of learned behavior, and the cues which are given for the prediction of the reward have been found to produce robust changes in the neural activity of NAcc (Day and Carelli 2007). In appetitive conditioning, when a CS has been associated with the appetitive outcome, such as food, it elicits the conditioned response of locomotor approach to CS, a phenomenon known as autoshaping. Anatomical studies of appetitive behavioral responses revealed the functional difference between the NAcc-core and NAcc-shell subregions. For example, excitotoxic lesions of the NAcc-core area resulted in impairment of acquisition of

an autoshaping appetitive behavior in rats (Parkinson et al. 2000b). In addition, the post-training NAcc-core lesion impaired the performance of conditioned response in rats. In contrast, the lesion of the NAcc-shell region did not impair the animal's appetitive behavior and responses against a conditioned reinforcement (Cardinal et al. 2002). Interestingly, depletion of dopamine in the NAcc induced impairments in both the acquisition and performance of autoshaping (Parkinson et al. 2002). Hence, it has been reasoned that the NAcc-core region may play a role in the modulation of conditioned behavior and NAcc-shell area may have a similar influence on behavior but in relation to unconditioned stimuli (Cardinal et al. 2003).

In general, the NAcc may have a role in forming associations between predictive cues and their outcomes. It may process the relative information about the unconditioned as well as conditioned aspects of Pavlovian learning which ultimately decides the animal's response toward rewards in their environment (Day and Carelli 2007). The NAcc along with other motivational areas such as the amygdala, hippocampus, and regions of the prefrontal cortex helps in regulating motivational outputs and represents an interface between limbic and motor areas (Cardinal et al. 2003).

9.8 The Orbitofrontal Cortex

The orbitofrontal cortex (OFC) is another key region, which plays an important role in appetitive conditioning. The strong anatomical connection of OFC and BLA suggests that both these regions work in coordination for the acquisition of new associations. Lesion studies suggest a dual function of OFC in associative learning. On the one hand, the OFC has a role in the encoding of outcome expectancies, and, at the same time, it also has the ability to augment associative learning in the BLA. For example, the OFC-lesioned animals exhibit normal conditioned responses, but they did not show normal conditioned attenuation after food devaluation (Baxter et al. 2000; Gallagher et al. 1999). These animals also demonstrate altered activity of the BLA neurons in response to outcome expectancy. These results suggest that the OFC plays an important role in outcome expectancies, which can be used for encoding the information of associative learning in the BLA circuitries (Schoenbaum and Roesch 2005; Schoenbaum et al. 2003b). In short, OFC represents the association between the CS and the current value of the US, which can be used by the BLA to encode the associative information. In neuroimaging studies on human, it has been observed that the OFC gets activated during appetitive conditioning. Although, these studies support the idea that the OFC could be one of the core areas that plays an important role in appetitive learning, more studies are, however, required to understand the role of different specialized sub-compartments of the OFC in appetitive conditioning.

9.9 The Ventral Tegmental Area

The ventral tegmental area (VTA) is a source of input to the brain areas associated with incentives and motivation (Swanson 1982). Inactivation of VTA has been found to impair the reward-directed behavior (Di Ciano and Everitt 2004; Yun et al. 2004). VTA afferents release dopamine to target areas, such as NAcc and prefrontal cortex (PFC), involved in reward consumptions and presentation of predictive reward cues (Day and Carelli 2007; Ito et al. 2002; Phillips et al. 2003; Roitman et al. 2004). The activity of the dopaminergic neurons in the VTA and substantia nigra increases after appetitive operant and Pavlovian conditioning tasks during the presentation of the reinforcer (Mirenowicz and Schultz 1994). However, as soon as the cue-reward association is learned by the animal, this excitatory response diminishes, and excitatory response to the new cue onset emerges (Ljungberg et al. 1992; Mirenowicz and Schultz 1994). The activation of dopaminergic neurons in the VTA enhances, whereas its lesion or inhibition tends to reduce the reward-seeking behavior (Cheer et al. 2007; Fields et al. 2007). These studies further suggest that the dopaminergic neurons of the VTA may have a role in positive reinforcement as well.

9.10 Neural Basis of Appetitive Conditioning

In appetitive conditioning, CS-associated response toward the presentation of US requires that the associated areas work in proper coordination in order to generate the behavioral outcome. This involves various neuromodulators, their receptors, and initiation of a signaling cascade that ultimately activates the interconnected neural circuitries in different brain regions during the conditioning tasks. Several reward circuitry-related studies have suggested the involvement of some neurotransmitters such as dopamine (DA), glutamate, serotonin, cannabinoids, and opioids and also neuropeptides such as orexin, leptin, and ghrelin, in homeostatic regulation of food intake during appetitive tasks (Atkinson 2008; Cason et al. 2010; Cota et al. 2006). Among these, DA is the most commonly studied neurotransmitter for reward circuitries in both invertebrates and vertebrates models. It has been found that VTA sends direct DA projections to NAcc and other brain regions such as the amygdala, hippocampus, caudate, putamen, orbitofrontal cortex, etc. (Fig. 9.3). During appetitive conditioning, exposure to food (for the first time) increases the firing of DA neurons in the VTA, resulting in an increased DA release in the NAcc (Norgren et al. 2006). Repeated exposure to the same reward (i.e., food) habituates the DA response (Epstein et al. 2009; Schultz 2010). Further, in a human imaging study, Volkow et al. (2011) have reported an elevated DA level in the striatum upon exposure to food-associated cues, which resulted in an increased desire for food consumption (Volkow et al. 2011). Besides DA, NAcc also receives glutamatergic

projections from the PFC, amygdala, hippocampus, and OFC (Geisler and Wise 2008; Russo and Nestler 2013). Glutamatergic inputs from the amygdala and OFC to the DA neurons in the NAcc are specifically involved in appetitive conditioned response (Petrovich 2011). Moreover, glutamatergic innervations also connect these areas reciprocally with each other (Russo and Nestler 2013).

In addition, GABA plays an important role in appetitive conditioning. The functional output of these areas is directly modulated by GABAergic interneurons (Tritsch et al. 2012). Interestingly, each of these areas also receives serotonergic and noradrenergic innervations from midbrain raphe nuclei and pontine locus coeruleus, respectively, which suggests a possible role of these neurotransmitters in appetitive behavior (Hnasko et al. 2012; Tritsch et al. 2012).

Among neuropeptides, leptin and ghrelin are known to have a crucial role in appetitive behavior in humans. It has been found that leptin influences the neural circuitries underlying food intake. In the congenital leptin-deficient patients, leptin replacement therapy induces neural activation in the striatal regions, which possibly diminishes the perception of food reward and enhances the response to satiety (Farooqi et al. 2007). It has also been found that leptin in the ventral hippocampus suppressed the memory for spatial location of food (Kanoski et al. 2011). On the other hand, ghrelin activates the reward-associated areas such as the amygdala, OFC, etc. in response to food stimuli and contributes in the development of seeking behavior (Malik et al. 2008; Russo and Nestler 2013).

Classical conditioning studies in invertebrate models such as *Drosophila* had demonstrated the essential role of dopaminergic and octopaminergic neuronal activities in the aversive and appetitive learning, respectively (Schwaerzel et al. 2003). Schroll et al. (2006) have shown that optogenetic stimulation of dopaminergic neurons resulted in odor-associated aversive memory formation, whereas activation of octopamine/tyraminergic neurons induces appetitive memory formation (Schroll et al. 2006). These studies suggest that two independent neural circuitries modulate the aversive and appetitive reinforcement during classical conditioning in insects.

In higher vertebrates, glutamatergic N-methyl-D-aspartate (NMDA) receptors and dopamine D1 receptor play an important role in inducing learning-dependent neuronal plasticity. NMDA receptor activation is crucial for long-term potentiation (LTP) in the hippocampus for various learning and memory forms including appetitive learning (Izquierdo and Medina 1997; Malenka 1994; Malenka and Nicoll 1993; Robbins and Everitt 1996). The microinjection of NMDA receptor antagonists in the amygdala and PFCs impaired appetitive instrumental learning (Baldwin et al. 2002). In another study, Dalley et al. (2005) have investigated the role of D1 and D2 receptor and NMDA receptor in the NAcc in appetitive learning. They found that infusions of both D1 and NMDA receptor antagonists soon after learning, but not delayed infusion, significantly impaired appetitive learning; however, D-amphetamine and the D2 receptor antagonists did not induce any impairment. These studies suggest that D1 and NMDA receptors in the NAcc play an important role in the consolidation of appetitive conditioning during the early phase (Dalley et al. 2005). In addition, these two receptors are involved in the induction of LTP and

other forms of neuronal plasticity underlying associative processes in learning (Floresco et al. 2001; Kelley et al. 2003; O'Donnell et al. 1999; Pennartz et al. 1993; Spencer and Murphy 2000).

The dopaminergic-mediated appetitive conditioning involves the activation of second messenger system. Stimulated D1 receptors activate adenylyl cyclase, which increases the production of cyclic AMP (cAMP). The downstream targets of cAMP are cAMP-dependent protein kinase A (PKA) (Browning et al. 1985; Kötter 1994), which plays a crucial role in memory consolidation and neuronal plasticity (Kandel 1989). It is elucidated that PKA may affect learning and memory via the phosphorylation of learning-associated transcription factor, cAMP-response element binding protein (CREB), which ultimately initiates the CREB-mediated gene transcription and allows the expression of various plasticity-related proteins required for memory formation (Silva et al. 1998). It has been observed that serine/threonine kinase inhibitor (which blocks the activity of protein kinase A, C, and G (Casnellie 1991)) disrupted instrumental appetitive learning (Rothermel and Parker Botelho 1988). The role of another class of protein kinases such as calcium-calmodulin-dependent protein kinase II (CaMKII) and various calcium-dependent isoforms of protein kinase C also play an important role in appetitive conditioning and involve CREB, a transcription factor (Silva et al. 1998). CREB is involved in the consolidation of several memory forms in different animal models. It is involved in the olfactory conditioning in flies, as well as in the appetitive and fear conditioning and spatial and social learning in mice. CREB is also involved in LTP induction and synaptic restructuring, which are believed to be crucial for memory formation.

9.11 Sleep and Appetitive Conditioning

A large number of studies consistently revealed the role of sleep in a variety of learning tasks such as declarative memory, procedural memory, spatial learning task, and aversive and appetitive conditioning. The significance of sleep in memory consolidation has been investigated by taking mainly two different approaches into consideration (a) influence of sleep deprivation on learning and (b) influence of learning on sleep. A number of studies have reported detrimental effects of sleep deprivation on memory consolidation (Chen et al. 2014; Chowdhury et al. 2011; Graves et al. 2003; Kumar and Jha 2012; Stickgold et al. 2001). In addition, previous reports suggest that learning a new task influences either specific sleep state (rapid eye movement (REM) or non-REM (NREM) sleep) or sleep components (Fogel et al. 2007; Hellman and Abel 2007; Kumar and Jha 2012; Smith and Rose 1996). Augmented sleep after learning could also be implicated in memory consolidation (Benington and Frank 2003; Stickgold et al. 2001). For example, rats living in an enriched environment exhibit an increased sleep amount compared to the animals living in an impoverished environment (Mirmiran et al. 1982; Tagney 1973). A

theory of REM sleep window for learning has also been proposed. Smith and Rose (1997) have found that REM sleep increases between a 1 and 4 h window after spatial learning of the Morris water maze, and if the animals are REM sleep deprived during the same time period, memory is altered. Hence, they proposed that augmented REM sleep within this window helps to consolidate spatial memory (Smith and Rose 1997). We have also found a similar change in REM sleep within a similar time window frame after learning an appetitive conditioning task (Tripathi and Jha 2016) and augmented NREM sleep after learning a cued fear conditioning task (Kumar and Jha 2012). Similar augmentation in sleep amount within the same time window did not occur when the cued fear-conditioned memory was altered (Kumar and Jha 2017). These studies support the view of a sleep window, during which, sleep amount is augmented after learning. The sleep window may have implications in memory consolidation. The neuronal activity in several brain regions, such as the striatum, hippocampus, and visual and prefrontal cortices, is replayed in a similar fashion during sleep as they fired during acquisition (Louie and Wilson 2001; Peyrache et al. 2009; Skaggs and McNaughton 1996). In addition, the replay largely co-occurs together with slow-wave ripples (Colgin 2016). The strong slow-wave ripples usually occur along with augmented sleep. Therefore, it is likely that the augmented sleep with strong slow-wave ripples would contribute in facilitating neuronal replay and in turn memory consolidation.

The link between sleep and memory has been found in lower animals too. In *Drosophila*, the mushroom body is a key area involved in sleep regulation (Joiner et al. 2006) as well as in memory acquisition and consolidation (Heisenberg 2003). In one interesting study, it has been reported that the hyperkinetic mutant flies exhibit both an altered sleep pattern and impaired learning abilities. This study had demonstrated strong genetic evidence that altered sleep is associated with poor memory (Bushey et al. 2007). Sleep deprivation in honeybees, however, did not affect the consolidation of new memory, rather it only affects the extinction memory (Hussaini et al. 2009). Hence, it was advocated that sleep deprivation can disrupt only the weaker memory, i.e., extinction memory, but not the strong memory, i.e., acquisition memory. It would require more in-depth studies to ascertain the distinctive role of sleep in memory consolidation. It is possible that the consolidation of some memories is sleep-independent.

Higher animals also demonstrate detrimental effects of short-term sleep deprivation on learning. Short-term sleep deprivation (total sleep or only REM sleep) immediately after training impairs memory consolidation. For example, post-training short-term sleep deprivation induces memory impairment of object recognition (Palchykova et al. 2006), visuospatial attention (Cordova et al. 2006), spatial learning (Alzoubi et al. 2012), and associative learning (Chowdhury et al. 2011; Graves et al. 2003; Kumar and Jha 2012) tasks. In addition, quantitative and qualitative changes occur in sleep architecture after learning various tasks. For example, NREM sleep and its components such as delta and sigma waves increase significantly after fear conditioning and motor learning task in rodents (Hellman and Abel 2007). REM sleep exclusively increases after learning negative and positive

reinforcement and avoidance, aversive, and appetitive conditioning tasks (Datta 2000; Smith and Rose 1997; Tripathi and Jha 2016; Walker 2009). These studies suggest that specific memory types may require optimal sleep amount either NREM or REM sleep after learning, which may favor memory consolidation.

9.12 The Role of NREM and REM Sleep in Appetitive Conditioning

Learning of an appetitive task may require various sleep stages. The tone responsiveness of the hippocampal, amygdalar, and auditory thalamic neurons enhances during REM sleep after appetitive delay conditioning (Hennevin et al. 2007). Therefore, it is likely that REM sleep may favor the induction of plasticity underlying associative conditioning (Hennevin and Maho 2005). Further, it has been noticed the CS induced conditioned response in the hippocampal-dependent trace conditioning and the hippocampal-independent delay conditioning is not expressed uniformly during NREM sleep (Wamsley and Antrobus 2009). For example, the participants trained for trace conditioning exhibit an increase in EEG's K-complex during NREM sleep in response to CS. The similar increase in EEG's K-complex during NREM sleep, however, has not been found in the participant trained for delay-conditioned task (Wamsley and Antrobus 2009). Also, the CS induces more negative emotions during dreaming in trace-conditioned participants than the delay-conditioned subjects (Wamsley and Antrobus 2009). We have reported recently that the appetitive conditioning did not influence NREM sleep or wakefulness; however, it causes a significant increase in REM sleep (Tripathi and Jha 2016). REM sleep, interestingly, increased significantly during an initial 4-h time window and returned to the basal level at the end of the 6-h period (Tripathi and Jha 2016). A similar increase in REM sleep within 1 to 4-h window after the spatial learning task has been reported (Smith and Rose 1996, 1997). In our study, we found that the number of REM sleep episode selectively increased on the training and testing days. Interestingly, REM sleep episode length and latency did not change. It demonstrates that the animals spent significantly more time in REM sleep, which was frequently appearing after learning the appetitive conditioning task (Tripathi and Jha 2016). Some learning tasks require augmentation of both sleep states, while some need either NREM sleep or REM sleep (Eschenko et al. 2006; Kumar and Jha 2012; Tripathi and Jha 2016; Walker 2009). It is not yet known why different learning tasks require different sleep states. Interestingly, it has been observed that sleep spindles, delta waves, PGO waves, and hippocampal theta waves play an important role in the induction of synaptic plasticity (Nader and Smith 2003). Since these sleep components appear during specific sleep stages, it is likely that the learning task, which would essentially need sleep state-specific induction of synaptic plasticity, would tend to trigger the same sleep state after learning.

9.13 The Effect of Total Sleep Deprivation in Appetitive Conditioning

Sleep deprivation, either total sleep deprivation or REM sleep deprivation, soon after training causes learning impairments. For example, total sleep deprivation soon after object recognition task training impaired the performance of the learned task at the time of testing (Palchykova et al. 2006). A similar effect was observed in visuospatial attention task (Cordova et al. 2006), spatial learning task (Alzoubi et al. 2012), and trace appetitive learning tasks (Chowdhury et al. 2011). It has been found in the Morris water and radial arm maze tasks that the selective REM sleep deprivation impaired reference memories; however, the visual cue and working memories remained unaltered after REM sleep deprivation (Smith and Rose 1997; Smith et al. 1998). These studies suggest that after memory acquisition, sleep facilitates and optimizes its consolidation at an explicit time window. We have recently reported that sleep plays an important role in the consolidation of delay-conditioned memory (Tripathi and Jha 2016). Short-term sleep deprivation soon after training significantly induced learning deficit in sleep-deprived animals. Animals in all groups (non-sleep deprived, sleep deprived, and stress control) exhibited comparable head entries in the juice-dispensing window during the training, which suggest that all animals had learned the task equally. The non-sleep-deprived and stress control animals exhibited significantly better performance during testing, while sleep-deprived animals performed significantly less during the testing, suggesting that sleep-deprived animals had difficulties in task recollection. The learning deficit in sleep-deprived animals can be attributed primarily to sleep loss and not to any stress because stress control animals exhibited similar performances during the testing as the NSD animals. Confinement stress in a restricted area in stress control animals did not cause sleep loss. Interestingly, they spent more time in NREM sleep. There are reports suggesting that exposure to some stressors may reduce sleep, whereas exposure to certain other stressors, for example, social defeat, learned helplessness, and short-term immobilization stress, may augment sleep (Pawlyk et al. 2008). However, in our study, we found that the stress control animals experienced relatively more NREM sleep compared to the animals housed in their normal environment. Our study is the only study so far, where we have studied the effects on memory after 6 h sleep deprivation and stress. We have demonstrated that memory deficit was due to sleep alteration only and not because of stress.

Sleep deprivation is one of the primary tools to investigate the role of sleep in memory consolidation. Using various sleep deprivation methods such as flowerpot technique, gentle handling, rotating platform method, and optogenetic stimulation, it has been shown that post-learning sleep deprivation results in memory deficits because of disruption in its consolidation (Fishbein 1971; Leconte et al. 1974). The hippocampus-dependent tasks have been found to be most vulnerable to sleep deprivation. It was first demonstrated by using the Morris water maze task. The Morris water maze task can be configured as “hippocampal-dependent” as well as “hippocampal-independent” models of spatial learning task (Morris et al. 1982). The

sleep-deprived animals trained for the hippocampus-dependent Morris water maze model showed memory deficit. However, the animals trained for the hippocampus-independent Morris water maze model exhibited no change in their performances after sleep deprivation (Smith and Rose 1997; Smith et al. 1998). Similar dissociated effects of sleep deprivation on the hippocampus-dependent and hippocampus-independent fear-conditioned memory have also been found (LeDoux 2000). The contextual fear-conditioned mice (a hippocampus-dependent configured task) exhibited memory deficit after sleep deprivation, but the cued fear-conditioned animals (a hippocampus-independent task) did not show memory impairment after sleep deprivation (Graves et al. 2003). Sleep deprivation performed prior to the learning of hippocampal-dependent and hippocampal-independent configured fear conditioning tasks also induced similar dissociated effects (Ruskin and LaHoste 2009; Ruskin et al. 2004). Memory remains sensitive to sleep deprivation during the initial phase but not during the late phase. It has been found that if animals are allowed to sleep soon after acquisition and are sleep deprived at later time point, the long-term memory remains intact. This suggests that sleep essentially plays a crucial role during the early phase of consolidation, while late consolidation phase seems to be sleep-independent (Graves et al. 2003; Palchykova et al. 2006).

How sleep helps in memory consolidation is not clearly known. But, it was found in several studies that sleep deprivation selectively impaired cAMP- and protein kinase A (PKA)-dependent forms of synaptic plasticity in the hippocampus (Vecsey et al. 2009). It has also been observed that cAMP signaling remains reduced but the expression level of phosphodiesterase 4 (PDE4) enzyme (which is involved in cAMP degradation) increases after sleep deprivation. Interestingly, the sleep-deprived animals treated with phosphodiesterase inhibitors did not demonstrate sleep deprivation-mediated alteration in cAMP signaling, synaptic plasticity, and hippocampus-dependent memory consolidation (Vecsey et al. 2009). The study suggests that cAMP could be the main target protein, which is primarily affected by sleep deprivation. Since cAMP plays an important role in memory consolidation (Nguyen and Woo 2003), therefore, it is likely that sleep deprivation alteration in memory consolidation could be affected mainly through the alteration of the cAMP level. Interestingly, sleep deprivation increases the activity of PDE4 and the expression of PDE4 isoform, suggesting the possible reason for sleep deprivation-mediated alteration in cAMP level. In our preliminary results, we have also observed that the alteration in cAMP and PKA level in the amygdala impaired appetitive memory (Tripathi and Jha 2017). Our preliminary results suggest that cAMP level in the amygdala is also involved in the consolidation of sleep-dependent appetitive conditioned memory (Tripathi and Jha 2017).

9.14 The Role of REM Sleep in Appetitive Conditioning

It has been found in some studies that REM sleep is a most favored state during the post-training period. It plays an important role in memory processing (Datta 2000; Dujardin et al. 1990; Fishbein and Gutwein 1977; Smith 1985). The tone

responsiveness of the hippocampal, amygdalar, and auditory thalamic neurons increases significantly during REM sleep after delay conditioning (Hennevin et al. 1993, 1998). It suggests that REM sleep somehow facilitates the processes of consolidation and neuronal plasticity of associative memory (Hennevin and Maho 2005). Interestingly, it has also been found that the dopaminergic reward system is activated during REM sleep. Many neurophysiological studies in animals have demonstrated that the regions of the dopaminergic system, such as the NAcc and VTA, show increased neuronal firing burst during REM sleep (Dahan et al. 2007; Lena et al. 2005). The lateral hypothalamic orexinergic system, which is also involved in REM sleep regulation, plays a crucial role in glutamatergic transmission in the VTA (Borgland et al. 2008) and also in reward-seeking and motivation to obtain food (Harris et al. 2005). These studies further support the view that REM sleep may be the most favorable and important sleep state, which would largely be required for the consolidation of appetitive conditioned memory.

9.15 Conclusions

In associative learning, it is important for an individual to predict the possible imminent events based on past experiences and accordingly express appropriate behavior. The individual learns to extract logical information of the conditioned stimulus to predict the potential outcomes. It happens because the conditioned and unconditioned stimuli are presented in a paired fashion during conditioning, and with repeated presentation, the conditioned stimulus gradually acquires the properties of the unconditioned stimulus and induces conditioned responses. How the acquired associative knowledge drives appropriate predictive behavior is not yet known, but it has been found that an association is formed at the neural level between the conditioned and unconditioned circuitries, which possibly induces a conditioned response. Also, neurons of the conditioned circuitry compete among themselves to encode associative memories, and the relative CREB activity in neurons at the time of learning becomes the determining factor. It allows them to participate in the competition or make them eligible to encode memory traces (Han et al. 2007). The acquired memory traces are then stabilized with time. The neurons that participate in the encoding of memory traces are periodically reactivated for offline processing during memory stabilization (Stickgold et al. 2001). Thus, the acquired labile memory is converted into long-term memory, preserved in the specific brain areas, and retrieved in the future depending on the need.

The studies about associative conditioning in lower animals have also contributed immensely to our understanding. It has been observed that distinct pathways participate in acquiring and processing the information of different memory types. For example, dopaminergic and octopaminergic neurons communicate the information of aversive and appetitive stimuli, respectively, to the central brain area, the mushroom body in *Drosophila*. Further, the cAMP signaling pathways also play an important role in appetitive conditioning in lower animals as well. These suggest

that common neurotransmitters/neuromodulators and neural circuitries could be involved in appetitive conditioning across different species.

Memory consolidation possibly involves two independent events (i) experience-mediated activation of cellular and molecular events, which induces synaptic alteration, and (ii) offline memory processing, during which, the memory traces are reactivated several times and possibly help in the encoding of information for long-term use. Many studies have pointed out that sleep facilitates both events at some specific time points. For example, short-term sleep deprivation soon after learning alters cAMP level as well as cAMP signaling in the brain. The cAMP signaling is essentially required for CREB expression, receptor recruitment, induction of synaptic plasticity, etc., which are primarily involved in memory consolidation. How sleep precisely contributes to synaptic strengthening after learning a task is not known, but the current knowledge suggests that sleep possibly facilitates memory consolidation through maintaining the cAMP signaling during the initial phase of memory consolidation.

Additionally, sleep facilitates the offline processing of memory consolidation. The brain areas engaged in learning are reactivated in a similar fashion during post-training sleep. The offline reactivation is considered to be very important in stabilizing the labile memory traces acquired during learning (Stickgold et al. 2001). In place-reward associations, the spatial and emotional learning components are replayed during sleep in the hippocampus and ventral striatum, but the replay in the hippocampus occurs shortly before the ventral striatum (Lansink et al. 2009). The near-synchronous activity at more than one brain areas during sleep supports the idea that sleep may help facilitate the information integration regarding place-reward associations (Lansink et al. 2009). It, however, remains unclear how this offline reactivation occurs during sleep. What could be the intrinsic neurosensory substrates involved in the initiation and orchestration of neural replay after learning are yet to be determined.

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